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The Meaning of Concordance and Discordance in Estimation of Penetrance and Gene Frequency[1]

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THE STUDY of hereditary traits in man is frequently complicated by incomplete penetrance. The resultant deviations interfere with the estimation of gene frequencies and may even obscure the mode of inheritance of some traits. A unit factor with relatively high penetrance will generally be recognizable in an adequate series of pedigrees, and the degree of penetrance can be estimated with some accuracy. However, if penetrance of the unit factor is markedly reduced, pedigree studies alone may be inconclusive. In such instances it would be desirable to have an independent estimate of the frequency of the susceptible genotype in the population.

The desired estimate may be obtainable from data on concordance and discordance between identical twins or, for morphological traits, between right and left sides of the body. For this purpose, certain formulas have been proposed by Danforth (1924), Schinz (1945), and Lasker (1947), all of them based upon one apparently simple principle. If a genotype expresses itself regularly, bilateral concordance or twin concordance is inevitable. If the expression of a trait may be prevented by one or more randomizing factors, discordance is expected occasionally, and in the limiting case the product of the discordant classes will equal that of the concordant classes. In the attempt to apply this principle, complications are encountered, some of which do not appear to have been recognized by previous authors.

I. GENERAL CONSIDERATIONS

It has been stated by Dahlberg (1942) and others that the concept of *incomplete penetrance* is often simplified to such an extent that the complex mechanisms of its origin are neglected. The dangers involved may be shown in relation to the problem which was dealt with by the previously mentioned group

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[1] This investigation was undertaken in connection with the Harvard-Ohio State Rimrock Navaho Study. Most of the work was done during tenure of a research fellowship from the National Institute of Health. Although assistance and advice were rendered by many people, the author wishes especially to thank Dr. J. N. Spuhler, Dr. F. J. Kallmann, and Dr. S. C. Reed.

of investigators. Their inference was that the factors determining non-penetrance of a gene were entirely random; it was assumed, therefore, that all correlation between right and left or between identical twins, with respect to the trait, could be ascribed to the shared genotype, and that concordance and discordance could be expected as in a random distribution. According to Dahlberg (1942), intra-uterine environmental factors were not apt to play an important part with respect to unilateral non-penetrance. However, both of these suppositions appear to be questionable.

That intra-uterine factors can be of major importance in mammalian genetics in regard to both concordance and discordance has been demonstrated by Wright's study of polydactyly in guinea pigs (1934). In an inbred stock which revealed no significant parent-offspring correlation, polydactyly was correlated to the extent of .59 for litter-mates, and .73 for sides of the body. This observation is important not only on account of the high degree of concordance in both cases, but also because of the increased discordance between individuals as compared with sides of the same individual, despite genetic uniformity.

Apparently, developmental processes are primarily random. Apart from being subject to the laws of thermodynamics, they take place on a biological level where at every moment multiple influences tend to randomize the sequence of events. In fact, two individuals of the same species, or two sides of the same individual, develop according to a common design only insofar as gene-controlled mechanisms reproduce the same conditions within and around the embryo. It is probable, therefore, that many processes remain partly uncontrolled, especially those which have no significance in adaptation. Non-adaptive asymmetries with a left or right preponderance are likely to represent the influence of the primary, adaptive asymmetries upon otherwise uncontrolled processes (Landauer, 1948). In general, then, most of the non-adaptive, right-left asymmetries can be ascribed to the tendency of embryonic development to be primarily random in nature.

Of course, symmetry and concordance are not entirely ascribable to genotypic similarity, much less to single genes. Many genetic data indicate the important effects of "genetic background" on the expression of traits produced by a single mutant gene. Investigations of phenocopies as well as Wright's previously mentioned data have demonstrated the significant influences of the embryonic environment on traits which are not completely determined by heredity. These influences tend to increase right-left or twin correlation. Therefore, any statistical method which aims at using the correlation in estimating the penetrance and frequency of a single gene should apportion it between the given unit hereditary factor and those other influences which may contribute to it.

It may be mentioned at this point that the methods to be presented have severe limitations which will be described later on (section IX). The present

discussion is offered merely as the first step toward a more adequate treatment of certain principles which are usually neglected in the analysis of traits distinguished by incomplete penetrance or asymmetry.

II. PHENOTYPIC STRUCTURE OF THE POPULATION

Any trait that may be present or absent is apt to divide a population into two well-defined phenotypes. If it is inherited with complete penetrance, the phenotype frequencies are usable in estimating gene frequencies. Without complete penetrance, estimates of gene frequencies are less accurate. Besides, if the trait is very common, incomplete penetrance of the character may be difficult to distinguish from incomplete penetrance of its suppression, although these alternatives correspond to entirely dissimilar gene frequencies (Fig. 1).

If a trait is incompletely penetrant and expressible unilaterally, it tends to divide the population into four phenotypes. The trait may be present

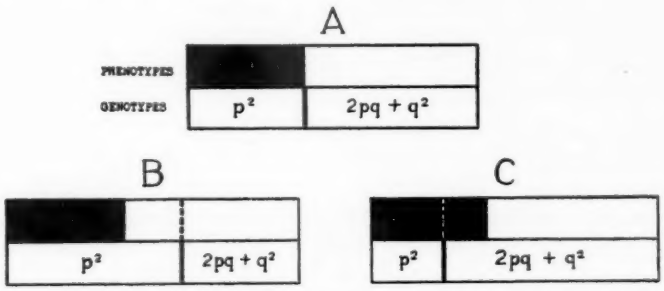

FIG. 1. Three gene distributions compatible with one distribution of phenotypes. A. Complete penetrance. B and C. Incomplete penetrance.

(a) bilaterally, (b) on the right, (c) on the left, and (d) on neither side. These four phenotypes, like those involving symmetrical traits with incomplete penetrance, fail to coincide with any genotypic divisions. In fact, the population may be essentially a single genotype, as in the case of Wright's polydactylous population of guinea pigs. In contradistinction to symmetrical traits, however, the given traits may be limited in their possible distributions by the underlying genotypic structure of the population, and this effect has been analyzed in the present study.

If the trait is determined largely by one or two genes, the population will be divided into two or more classes with different frequencies of the trait, and the frequencies may be anywhere from zero to 100 percent. The resultant classes will be analogous to the phenotypes for traits with complete penetrance, and it is clear that if they can be estimated, they can be used like the conventional phenotypes of figure 1(A). For convenience and from analogy, these classes will be referred to as *population-phenotypes* or, simply, *population-types*. A

population-phenotype is here defined as *a subdivision of the population which manifests a trait with a characteristic frequency determined by a common gene or combination of genes*. The present analysis deals only with populations which are divisible into two population-types, presumably on the basis of a completely dominant gene and its recessive allele, either sex-linked or autosomal.

It appears advisable to restrict the discussion to cases in which the frequency of the trait is zero in one class. With respect to gout, for instance, men with the dominant gene apparently develop the disease in about 20 percent of the cases, while the frequency of gout in persons without the gene is assumed to be zero. If the two population types are designated x and z, z stands for the homogeneous type (e.g., people without the gene for gout) and x represents the genotype or genotypes with incomplete penetrance. Using a more precise interpretation of penetrance, one may say that x refers to that segment of the population which is genetically capable of manifesting the trait if there is no interference by other factors. Similarly, z includes individuals who will not develop the trait even in the presence of genetic modifiers or normal variations of the environment. The term "trait" will be used here only in reference to the condition having incomplete penetrance; thus attention may be focused upon the *absence* of a structure, or upon *immunity* to a disease. When it is not clear from pedigrees which condition has incomplete penetrance, both alternatives should be considered in turn.

Consequently, the population to be analyzed genetically is one containing four phenotypes with respect to a bilateral trait, which is assumed to depend largely on a dominant or recessive factor. If the trait is not genotypically asymmetrical (Dahlberg, 1943), the population is apt to show a positive correlation between right and left sides of the body because of both common environment and common inheritance, especially of the principal genes concerned. The first task, therefore, is to distinguish the correlation due to the postulated unit factor from that due to the environment or to modifying genetic factors.

III. EFFECT OF A UNIT FACTOR IN PRODUCING CONCORDANCE

For the purposes of a first analysis it may be conveniently assumed that all the observed right-left correlation is due to the postulated unit factor. The inference would be that expression of the trait is not affected by genetic modifiers or by environmental factors common to right and left sides. By definition, no correlation would in this instance be observable within the variable population-type, x. If y represents the fraction of x with bilateral non-penetrance (Fig. 2), only one value of y corresponds to no correlation. This value is found to satisfy the equation $bc = ay$, or $y = bc/a$, which is the formula used by Danforth. Thus, an estimate of the frequency of the population-phenotypes may be obtained from the observed phenotype frequencies as follows:

$$x = a + b + c + \frac{bc}{a}, \qquad z = d - \frac{bc}{a} \tag{1}$$

These formulas provide two different estimates that exactly fit the observations. For the data given in table 1 and figure 2, it is first assumed that *presence* of the feature has incomplete penetrance. In this case, the phenotypes should be lettered as follows: $a = .4$, $b = .3$, $c = .1$, $d = .2$. According to the formula (1), $x = .875$, $z = .125$. The gene frequencies are computed from the square root of x or z, depending on whether the trait acts like a recessive or a dominant.

If it is *suppression* of the feature that sometimes fails, the gene associated with the feature will be less frequent, instead of more frequent than the feature. For equations (1) to remain valid, a must now be applied to the phenotype showing bilateral suppression. The values to be substituted in the equations

FIG. 2. A Mendelian population with a bilateral trait sometimes expressed discordantly. Right-left correlation due entirely to a unit factor. Alternate solutions making $bc = ay$.

TABLE 1. HYPOTHETICAL DISTRIBUTION OF A MORPHOLOGICAL FEATURE IN A POPULATION SAMPLE OF 100

	PRESENT ON LEFT	ABSENT ON LEFT
Present on right	a 40 d	b 30 c
Absent on right	c 10 b	d 20 a

are $a = .2$, $b = .1$, $c = .3$, $d = .4$, and the result will be: $x = .75$, $z = .25$. Evidently, the gene frequencies will be different, too. These two approaches were used by Lasker in an attempt to obtain upper and lower limits for the gene frequency in a population in which a trait is thought to occur in both population-types.

In the kind of population which is under analysis here, the probability of the trait on the right is a plus b; on the left, a plus c. The *penetrance* of the trait is its probability within x, i.e., within the population-type which is capable of developing it. If t_1 and t_2 represent the unilateral penetrances on right and left, respectively,

$$t_1 = \frac{a + b}{x}, \qquad t_2 = \frac{a + c}{x} \tag{2}$$

This definition of penetrance is important for subsequent derivations and can be used in the present instance after evaluating x. However, the same result can be arrived at directly and more simply. If there is no correlation within the variable population type, the individuals affected on the right side should be a representative sample of the whole population-type, providing, therefore, a direct estimate of penetrance on the left. Thus, without knowledge of the size of the variable population-type, the two unilateral penetrances may be computed as follows:

$$t_1 = \frac{a}{a + c}, \qquad t_2 = \frac{a}{a + b} \tag{3}$$

If the incidence on the two sides is not significantly different, one may use the mean, $(b + c)/2$, which will be designated b'. Then, unilateral penetrance becomes

$$t = \frac{a}{a + b'} \tag{3a}$$

Similarly, it is possible to rewrite formulas (1) and (2) for cases in which there is only one parameter for penetrance:

$$x = a + b + c + \frac{b'^2}{a}, \qquad t = \frac{a + b'}{x} \tag{1a, 2a}$$

Total penetrance, that is, the probability of an individual of the required genotype showing the trait at all, may be defined in terms of the variable population-type, x, as was done for unilateral penetrance in (2):

$$T = \frac{a + b + c}{x} \tag{4}$$

Alternatively, total penetrance may be derived from the estimates of unilateral penetrance:

$$T = 1 - (1 - t_1)(1 - t_2) \tag{5}$$

$$\text{or } T = 1 - (1 - t)^2 \tag{5a}$$

Even if no real meaning is attached to them in a given case, the two parameters for unilateral penetrance and the estimate of the variable population-type are sufficient to describe the observed distribution. In order to reconstruct the distribution from the parameters, one may proceed as follows:

$$\begin{aligned} a &= t_1 t_2\, x \\ b &= t_1(1 - t_2)x \\ c &= t_2(1 - t_1)x \\ d &= (1 - t_1)(1 - t_2)x + 1 - x \end{aligned} \tag{6}$$

If the discordant classes are equal, one observes:

$$\begin{aligned} a &= t^2x \\ b + c &= 2t(1 - t)x \\ d &= (1 - t)^2x + 1 - x \end{aligned} \tag{6a}$$

Thus, with the numerical example of table 1, the estimates for one hypothesis are $t_1 = .8$, $t_2 = .57$, $x = .875$. By substituting these values into (6) and multiplying them by n, one obtains the frequencies of table 1.

Formulas (1) and (3) are essentially the same as those given by Danforth, Schinz and Lasker. They are of very little use if a significant part of the right-left (or twin) correlation is due either to environment or to minor genetic factors, or if three or more population-phenotypes are involved.

IV. EFFECT OF MODIFYING FACTORS AND ENVIRONMENT

The method described in section III deals with what may be regarded as a limiting case, namely, a population in which the effects of minor genetic factors and of environmental influences common to the two sides are zero. As a limiting case at the other extreme, a population may be considered which is uniform with respect to the unit factor, and in which the entire right-left correlation is due to minor factors. The average probability of the trait on the right and on the left may be computed, as before, from a plus b and a plus c. However, these values become identical with right and left penetrance as defined in equations (2), because the variable population-type now constitutes the entire population. If the activity of the controlling factors approximates a normal distribution, it would be correct to describe them by Pearson's coefficient of tetrachoric correlation. With these three parameters, two for penetrance and one for correlation, the distribution is again completely described. Thus, for the example previously cited, if $x = 1$, the unilateral penetrances are .7 and .5, and the tetrachoric correlation coefficient is .36.

For the purpose of reconstructing the observed distribution as in section III, the tetrachoric correlation is rather unwieldy. It appears preferable, therefore, to use what may be called the *correlation fraction*, or g, since it is simpler both conceptually and algebraically. This statistic is defined as the ratio of the excess of concordant individuals to the total expected discordant individuals. In other words, it is *the fraction by which the expected discordant classes are reduced in the observed distribution*. When based upon the total population, this fraction is easily computed from a 2×2 table by subtracting the observed from the expected discordants and dividing by the expected. In terms of the symbols used before, this operation is represented by the general formula:

$$g = \frac{ad - bc}{ad - bc + b'} \tag{7}$$

or, if the discordant classes are equal, by the formula,

$$g = \frac{ad - b'^2}{ad - b'^2 + b'} \tag{7a}$$

In a particular case, the statistic, g, should be regarded only as an arbitrary measure of correlation. Strictly interpreted, however, it implies that factors for correlation alter individuals who tend to be discordant; as a result, a fraction of them, g, become concordant and fall equally into the two concordant classes (Fig. 3). The relation between the *correlation fraction* and the coefficient of tetrachoric correlation is approximated by the formula, $r = 1 - (1 - g)^2$. As an approximation to Pearson's exact coefficient, this formula is simpler than those usually used, and is reliable over a wide range of correlations.

If one uses the correlation fraction as the measure of correlation, together with t_1 and t_2 for unilateral penetrance, reconstruction of the observed distribution becomes easy. The only step required is the addition or subtraction of a single term from all the expected class frequencies. According to the original

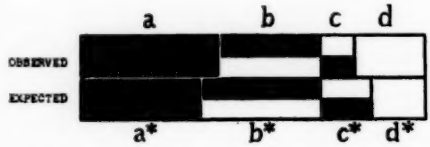

FIG. 3. Non-Mendelian population (uniform genotype) with trait expressed bilaterally. Distribution as in figure 2, but explained on the basis of environmental and minor genetic differences.

definition, g is exactly the fraction to be deducted from the expected discordant classes and to be added to the concordant classes. The two expected discordant classes are $t_1(1 - t_2)$ and $t_2(1 - t_1)$, and, since the correction for each is to be based on the *total* of expected discordants, the correcting term is $\frac{1}{2}g[t_1(1 - t_2) + t_2(1 - t_1)]$. If G is taken to represent this term, the observed distribution is given by the expressions (cf. equations 6),

$$\begin{aligned} a &= t_1t_2 + G \\ b &= t_1(1 - t_2) - G \\ c &= t_2(1 - t_1) - G \\ d &= (1 - t_1)(1 - t_2) + G \end{aligned} \tag{8}$$

When $t_1 = t_2$, the correcting term reduces to $gt(1 - t)$, so that the class frequencies may be obtained as follows:

$$\begin{aligned} a &= t^2 + gt(1 - t) \\ b + c &= 2t(1 - t)(1 - g) \\ d &= (1 - t)^2 + gt(1 - t) \end{aligned} \tag{8a}$$

V. CORRELATION WITHIN THE VARIABLE POPULATION-PHENOTYPE

In a population which is somewhere between the limiting cases discussed in the preceding two sections, part of the observed right-left correlation would be due to environment and minor genetic factors, and the remainder might be due to differences at a single genetic locus. Here, as in section III, one population-phenotype is assumed to be incapable of developing the trait, while the other contains both penetrant and non-penetrant individuals in four phenotypes. Within the variable type, x, one encounters the same problems of correlation and penetrance as were dealt with in Section IV.

Since treatment of the present problem is practicable only in cases in which b and c are approximately equal, further discussion will be limited to such cases. The desired solution would be attained by correcting the observed classes to eliminate correlation within the variable population-type, and by then applying the formulas of section III (Fig. 4). The resulting expressions will still con-

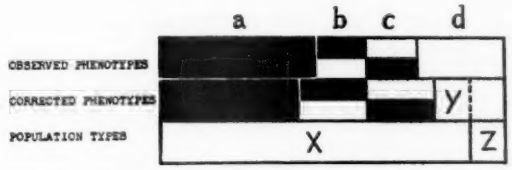

FIG. 4. Mendelian population with trait expressed bilaterally. Distribution within the population-type x shows correlation due to environmental and minor genetic differences.

tain two unknown parameters, and estimation of these will be discussed in sections VI and VII.

In the following equations, the expected classes (which are to be obtained by correcting for correlation) will be distinguished from the observed classes by an asterisk. The desired corrections are specified by the definition of the correlation fraction; the observed deficiency of discordant individuals divided by the expected discordant individuals is equal to g:

$$g = \frac{(b^* + c^*) - (b + c)}{b^* + c^*}$$

Since for the purposes of this discussion the discordant classes are equal, the equation becomes,

$$g = \frac{b^* - b'}{b^*}$$

When this is solved for b^*, the expression represents one expected discordant class:

$$b^* = \frac{b'}{1 - g} \tag{9}$$

Through addition and subtraction of gb' in the numerator, the right-hand member becomes a sum:

$$b^* = b' + \frac{gb'}{1 - g} \tag{10}$$

The correcting term, $gb'/(1 - g)$, represents one-half of the observed deficiency of discordants in the variable population-type, and one-half of the excess of concordants. As before, the excess is assumed to be distributed equally between the two observed concordant classes, so that the same correcting term may be used for these classes:

$$a^* = a - \frac{gb'}{1 - g}, \qquad d^* = d - \frac{gb'}{1 - g} \tag{11}$$

It is now possible to manipulate the four corrected frequencies, a^*, b^*, c^*, and d^*, just as the observed frequencies were manipulated in section III. The earlier equations take the form,

$$a^* y = b^* c^* \qquad y = \frac{b^* c^*}{a^*}$$

$$x = a^* + b^* + c^* + \frac{b^* c^*}{a^*}$$

The corrected classes can be replaced with expressions involving observed frequencies and the unknown correlation fraction if one uses formulas (9, 10, 11) and the relations,

$$c^* = b^* \qquad 2b' = b + c$$
$$a^* + b^* = a + b'$$

The resulting formula for the variable population-type is

$$x = a + b + c + \frac{gb'}{1 - g} + \frac{b'^2}{(1 - g)[a(1 - g) - gb']} \tag{12}$$

The probabilities of the three phenotypes can be expressed in terms of the parameters, x, g, and t, with equations resembling (6a) and (8a):

$$\begin{aligned} a &= t^2 x + gt(1 - t)x \\ b + c &= 2t(1 - t)\,(1 - g)\,x \\ d &= (1 - t)^2 x + gt(1 - t)x + 1 - x \end{aligned} \tag{13}$$

These equations are useless for the maximum likelihood method of estimation in the present case, because an infinite number of exact solutions exist. In a simplified scheme, however, the given equations serve to illustrate the way in which a unit genetic factor may interact with other sources of right-left correlation.

VI. APPORTIONMENT OF THE CORRELATION WHEN PENETRANCE IS SEX-INFLUENCED

The population data described in preceding sections do not contain enough information to permit apportionment of the correlation between the major unit factor and the remaining combination of genetic and environmental factors. Many traits with reduced penetrance are found to be more frequent in one sex than the other. This disproportion may be due to a sex-difference in penetrance, to sex-linkage, or to both. Under such circumstances, the parameters can be estimated by relatively simple methods if the volume of the data is sufficiently large. Let us first consider an autosomal trait with unequal penetrance in males and females.

Formula (12) shows that the relationship between population-type, x, and correlation, g, is independent of the penetrance, under the assumptions already discussed. The population-phenotypes are determined by the gene-frequency, which should be the same in the two sexes. It would also be reasonable to expect similar correlations in the two sexes. Hence, the two parameters, x and g, can be determined if male and female data are substituted separately into (12) and the resulting equations solved simultaneously. Algebraically, this process is rather tedious, so that it is advisable to use the simpler graphical solution. The equation results in a hyperbolic type of curve which, if plotted with g as the abscissa and x as the ordinate, is concave upward and to the left and has the asymptotes, $x = a + b'$ and $g = a/(a + b')$. The curve intersects the x-axis at the value of x given by formula (1a), and intersects the line, $x = 1$, at the value of g given by formula (7a). These intercepts represent the limiting cases discussed in sections III and IV, respectively. Apparently, the curves do not intersect more than once in the range of possible values, so that it is possible to determine from the intercepts alone whether or not a given hypothesis will yield a solution. When the curves for the female data and for the male data are known to intersect, two or three well-chosen points on each curve will give the estimates for x and g to two-place accuracy, and penetrance for each sex may then be computed by formula (2a).

In order to illustrate the method, fictitious data may be assumed to have been collected for 1000 males and 1000 females of a population in which a bilateral trait is widely distributed (Table 2). Considering first the hypothesis that *presence* of the feature has reduced penetrance, one letters the table from left to right and from top to bottom, as is usual in a 2×2 table. The results are shown in Table 3. Inspection of the intercepts reveals that the curves will not cross (Fig. 5a). In order to test the hypothesis that the trait with reduced penetrance is *suppression* of the feature, the data of Table 2 are re-labeled from right to left and from bottom to top (Table 4). It will be observed again that the curves do not intersect. It may be concluded, therefore, that the data do not seem to represent a completely dominant autosomal trait. Of course, this does

not preclude the possibility of a maximum likelihood solution, expanding equations (13) to utilize male and female data separately. In view of the large number of observations, however, such a solution would almost certainly fail to fit the data closely enough. Among the remaining possibilities, only that of a simple, sex-linked factor can be tested by the present methods.

TABLE 2. HYPOTHETICAL DISTRIBUTION OF A MORPHOLOGICAL FEATURE IN A POPULATION SAMPLE OF 2000

	FEMALES: LEFT SIDE		MALES: LEFT SIDE	
	present	absent	present	absent
Present on right	a 354 d	b 95 c	a 260 d	b 138 c
Absent on right	c 93 b	d 458 a	c 142 b	d 460 a

TABLE 3. FREQUENCIES AND INTERCEPTS UNDER FIRST HYPOTHESIS

	FEMALES	MALES
a	.354	.26
b + c	.188	.28
d	.458	.46
b′	.094	.14
x-intercept	$x_f = .567$	$x_m = .615$
(x = 1)-intercept	g = .62	g = .417

TABLE 4. FREQUENCIES AND INTERCEPTS UNDER SECOND HYPOTHESIS

	FEMALES	MALES
a	.458	.46
b + c	.188	.28
d	.354	.26
b′	.094	.14
x-intercept	$x_f = .665$	$x_m = .783$
(x = 1)-intercept	g = .62	g = .417

VII. ESTIMATION OF THE PARAMETERS WHEN THE TRAIT IS SEX-LINKED

The method used in testing for a sex-linked factor is almost the same as the one described in the preceding section. Instead of solving for *equality* of population-types in males and females, $x_f = x_m$, the desired solution is either $x_f = x_m^2$ or $x_f = x_m^2 + 2x_m z_m$, depending on whether the trait is recessive or dominant. The curve for x_f remains the same as before, but for the males it is necessary to plot the approrpiate *function* of x_m. Here again, the intercepts are ex-

pected to tell whether or not there is an exact solution, with perhaps rare exceptions in the case of a dominant trait.

Returning to the numerical illustration and the frequencies of table 3, one obtains two new x-intercepts for the male data as the appropriate functions of the original intercept: $x_m^2 = .379$ and $x_m^2 + 2x_m z_m = .852$. The $(x = 1)$-intercept (from formula 7a) is necessarily the same for all three curves. Intercepts are plotted in figure 5A, and they make it apparent that the curve for x_m^2 must cross that for x_f, whatever its course. Two values of x_m^2 can be calculated with the aid of formula (12) and a slide rule:

When $g = .2$, $x_f = .607$; $x_m = .711$; $x_m^2 = .506$
When $g = .4$, $x_f = .689$; $x_m = .960$; $x_m^2 = .922$

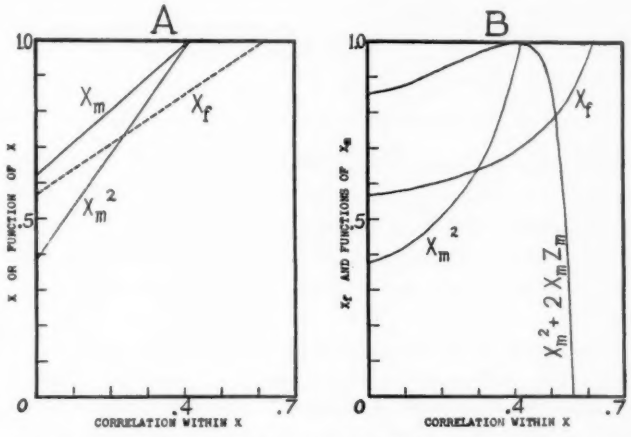

FIG. 5. Graphical solution for sex-linked trait (data of table 2). A. Use of intercepts as preliminary test. B. Curves used for estimation of the parameters.

If the curves are sketched, as is done in figure 5B, the intersection appears to be at about $g = .3$, $x = .65$. A final computation for $g = .3$ shows that the intersection is almost exactly here, with $g = .3$, $x_f = .64$, $x_m = .8$. These values refer to right-left correlation in the variable type, frequency of the variable type in females, and frequency of the variable type in males, respectively. The gene-frequencies are equal to the population-type frequencies in the males, so that the frequency of the gene producing the trait, p, is 0.8. The only remaining task is that of computing the penetrance for each sex. Using formula (2a) and the frequencies of table 2, one obtains the following values: $t_f = .448/.64 = .7$; $t_m = .4/.8 = .5$. According to formula (5a), total penetrance is 81% in females and 75% in males.

Even after an exact solution is obtained, it is advisable to test all the re-

maining hypotheses compatible with the known behavior of the trait in pedigrees, because it is possible that there may be two or more exact solutions. Plotting the male data for the hypothesis of a sex-linked dominant results in the uppermost curve in figure 5B, which intersects the curve for the female data only at $g = .52$, corresponding to $x_m = 1.5$, an impossible value.

Based on the hypothesis that the trait with reduced penetrance is suppression of the feature, the data of table 4 give a set of curves which are very much like those obtained from table 3, but with different x-intercepts. Again, an exact solution is found for the hypothesis of a sex-linked recessive, but now ***suppression*** is recessive, and the feature is dominant. The parameters obtained are $g = .17$, $x_f = .70$, $x_m = .84$, $t_f = .79$ and $t_m = .72$. The apparent frequency of the gene associated with presence of the feature is 0.16, instead of the value 0.8 found in the first solution. With such a wide difference in the estimates of gene-frequency, very limited family data should suffice to eliminate one of the two solutions.

VIII. APPLICATION OF THE METHOD TO TWIN DATA

The foregoing discussion has been specifically in reference to traits which occur bilaterally and, therefore, are expected to be concordant or discordant within one individual. The same principles apply to a qualitative trait to be studied in an unselected population of identical twins. The appropriate formulas are those given in section V in addition to the ones which have numbers followed by "a".

In twins, the formulas for *unilateral* penetrance of the bilateral traits refer to penetrance in the *individual*. Analogously, the formulas relating to *total penetrance* would apply to pairs of twins. If the traits have a higher or lower incidence among twins than among non-twins, the estimate of penetrance cannot be applied to the general population. In the absence of phenocopies, however, it may be assumed that mode of inheritance and gene-frequency are the same in twins and in non-twins. Accordingly, an estimate of penetrance in non-twins can be obtained with the formula,

$$\text{Penetrance} = \frac{\text{Frequency of the trait in the population}}{\text{Frequency of the variable type in twins}} \qquad (14)$$

The use of an uncorrected twin concordance rate as an estimate of penetrance would seem to be questionable from a mathematical standpoint. In the terminology used here, the implied formula is as follows:

$$\text{Concordance rate} = \frac{a}{a + 2b'} \qquad (15)$$

Evidently, this quantification falls short of the value of penetrance given by formula (3a):

$$t = \frac{a}{a + b'}$$

Formula (3a) constitutes the upper limit of penetrance for a unit factor producing an observed concordance rate. Its variance, derived by Winsor in a note appended to Lasker's paper, can be expressed as follows:

$$V_t = \frac{(1 - t)(2 - t)}{2\left(A + 2B' + \frac{B'^2}{A}\right)} \tag{16}$$

In this formula, A and $2B'$ represent the observed *numbers* of concordant and discordant affected pairs, repsectively. The lower limit of penetrance is the incidence of the trait in the population as a whole. Ordinarily, therefore, the

TABLE 5. UPPER LIMITS OF PENETRANCE COMPATIBLE WITH OBSERVED CONCORDANCE RATES

CONCORDANCE RATE	MAXIMUM PENETRANCE	
(bilateral or in MZ twins)	from twin data	right-left data
10%	22%	40%
20	33	56
30	46	71
40	57	82
50	67	89
60	75	94
75	86	98

concordance rate will fall within this range of penetrance, although it may be found under different circumstances that either limiting value will be more nearly correct.

The significance of these principles can be demonstrated with the data of Herndon and Jennings (1951) on poliomyelitis in twins. The concordance rate observed in 14 MZ index pairs was 35 percent. If it is assumed that a unit factor is responsible for the given trait, the lower limit of penetrance is under one percent (which would be compatible with a nearly universal distribution of the factor). In the absence of extraneous sources of correlation, the upper limit given by the twin data is 53 percent, with a standard error of nearly 10 percent. It follows that the data are compatible with the estimate of 70 percent penetrance given by Addair and Snyder (1942). For the purpose of testing the hypothesis of unit factor inheritance, the figure of 35 percent is little better than any arbitrary value.

Table 5 shows the maximum expected value for penetrance corresponding

to various concordance rates for traits which depend upon a specific gene or genotype. The second column shows penetrance as computed from twin data with formula (3a), while the right-hand column represents *total penetrance* according to (5a). This table presupposes both accurate estimation of the concordance rate and incomplete penetrance of the given trait, rather than of its alternative in the population, while it neglects a possible discrepancy in penetrance between twins and the general population. Obviously, penetrance can be higher than these limits if there is negative, rather than positive, correlation within the variable population type, between twins or between sides of the body.

IX. ASSUMPTIONS AND LIMITATIONS INHERENT IN THE METHOD OF ESTIMATION

It is apparent that the refinements which have been discussed in the preceding sections will enhance the accuracy of the original formula given by Danforth for estimating the frequency of non-penetrant individuals. However, the resulting method is still far from accurate unless certain conditions are met. Unfortunately, the postulated requirements do not seem to be fulfilled by any data currently available in human genetics, although statistics on the palmaris longus muscle approach them rather closely. The trait to be studied should have the following characteristics:

(1) It should be either a bilateral morphological character or a qualitative trait occurring in a population of MZ twins.

(2) The trait should be relatively frequent. The method requires data on affected and unaffected individuals in proportion to their occurrence in the population; it would therefore be difficult to gather adequate data on an uncommon condition unless it was so severe as to insure accurate and complete reporting to health authorities. Even in the latter case, many instances of both concordance and discordance would be required.

(3) It should be significantly more frequent in one sex than in the other.

(4) If a bilateral trait is studied, its incidence on right and left should be nearly equal, since the method of correcting for correlation is probably inaccurate when the two discordant categories are very unequal. This consideration would seem to have little or no bearing upon the use of the method with twin data, since there is no important, constant distinction between twins.

In order to study such a trait, it would be necessary to secure a large random sample of a population which is genetically rather homogeneous. A thousand individuals or twin pairs would seem to be the smallest number that could give useful estimates, everything else being optimal.

If these conditions are met, the estimates obtained depend upon several assumptions which are probably not universally valid. Therefore, the important check on the estimates is not their own standard error, but a test in a collection of family data. The assumptions are as follows:

(1) If sex has an effect on penetrance, it does not alter the intensity of right-left or twin-pair correlation. However, this assumption is needless in those cases of sex-linkage in which the method yields similar estimates of penetrance for both sexes.

(2) The probability of the trait is practically uniform within the variable population-type. This statement, means, for example, that if a variable type is produced by a dominant gene, penetrance is expected to be identical in homozygotes and heterozygotes. Also, the activity of minor factors is assumed to be distributed almost normally.

(3) The influences producing correlation, aside from the main gene, alter all four phenotypes by numerically similar increments or decrements. This assumption seems reasonable, if correlation within the variable type is not produced mainly by one or two factors acting always in the same direction; i.e., if assumption (2) is correct.

(4) The trait does not occur at all in one of the two population-types.

(5) Right-left or twin-pair correlation within the affected population-phenotype is not negative.

(6) Estimation of gene-frequencies by this method presupposes that the two population-types owe their difference to a single genetic factor, with respect to which the population is nearly in genetic equilibrium.

Assumption (2) excludes the class of traits, probably numerous, in which penetrance is appreciably higher in homozygotes than in heterozygotes. Assumption (4) means that the method may fail in the analysis of any trait which occurs occasionally in the "resistant" genotype. However, these two important categories of hereditary traits might lend themselves to analysis by other methods analogous to the one presented.

X. SUMMARY

Various authors have proposed formulas for estimating penetrance from concordance rates in traits which occur on the two sides of the body or in identical twins. It is indicated by careful consideration of the phenomena involved that such estimates should make allowance for correlation due to environmental and modifying genetic factors. By and large, simpler formulas are useful only in setting an *upper limit* for the penetrance which is to be expected on the basis of any observed concordance rate.

By making several simplifying assumptions, one can obtain equations which express the interaction of a dominant hereditary factor with other sources of right-left or twin correlation. These formulas can be used in estimating penetrance and gene-frequency with respect to traits which show a sex difference in incidence, irrespective of whether this difference is due to sex-linkage or to a sex difference in penetrance. The applicability of the method is limited to large bodies of data on traits which meet a number of statistical specifications.

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Selection and the Age Incidence of Human Cancer

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THE AGE DISTRIBUTION of morbibity and mortality from cancer varies greatly with different types and sites of malignant tumors. The causes of this variance are of considerable interest to clinicians, pathologists and geneticists, but no really satisfactory explanation of the phenomenon had been offered in the past.

In a recent lecture, however, Julian Huxley (1951) made the following statement which we quote in full:[1] "As a human illustration of the power of selection we may mention the age-incidence of human carcinoma. It is no longer in doubt that there is a genetic basis for the propensity to form malignant tumors, including the time of life at which they tend to develop. In women, reproduction ceases after about 45; and in all human societies up to quite recent times, the expectation of life was so low that very few men reproduced themselves at higher ages. Accordingly, since natural selection operates through differential reproduction, it can work on the possession of early-occurring but not on those of late-occurring (post-reproductive) tumors. The result is visible in the fact that the incidence of carcinoma is very low in youth and early middle age, but shows an enormous rise between 40 and 50. This rise does not occur with sarcomas, which are so comparatively rare that selection cannot act powerfully upon them."

This sounds like an eminently reasonable hypothesis. We have searched the literature in vain, however, for evidence which would support it. Since hypotheses tend to be the more readily accepted and are the more often treated as facts on which further hypotheses can be built, the more convincing they sound, we decided to test the validity of Huxley's hypothesis by an analysis of data on cancer mortality in the United States.

Our principal source of data were the excellent reports on "Cancer Mortality in the United States" published by the National Office of Vital Statistics of the U. S. Public Health Service (1950). Supplementary information was drawn from a publication by Gover (1941).

If the argument is valid that in the common types of carcinoma selection has shifted age at death beyond the reproductive period, and if the rare types of malignancy have to a greater or lesser extent escaped such effects of selec-

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[1] With permission of The Macmillan Company.

tion, then one should be able to detect the results in a comparison between the more common and the rare types of carcinoma and other malignant tumors as well as between carcinoma and sarcoma. To this end we have used the data on number of deaths from cancer of various sites for 1941 through 1945 and for the white population of the United States, as reported by the National Office of Vital Statistics. We did not use the data for the "nonwhite" group since there is good reason to believe that reporting for this group was less complete and diagnosis less reliable (Dorn, 1944). The data for adrenal, bones and thyroid (sites 55 a, b and c), which did not separately appear in the Vital Statistics Reports, were provided (for the year 1942) by the National Office of Vital Statistics. For each site we determined the percentage of deaths which, out of the total mortality, had occurred from 45 years of age on. Annual death rate per 100,000 was determined on the basis of the white male and female population estimates for July 1, 1943, as reported by the Bureau of the Census. This date was chosen because it was the midpoint of our 5-year period. In calculating the death rates of males we used the population estimates which include armed forces overseas, since it may be assumed that the great majority of the relatively few men who died from cancer while serving in the armed forces were returned to this country prior to death and hence are included in the mortality statistics. The results of our calculations are shown in table 1 for males and in table 2 for females. The data are arranged according to sites as they appear in the International List of Causes of Death.

The data for the specific sites, given in tables 1 and 2, are shown graphically in figures 1 and 2. The bars indicating the percentages of deaths occurring for each specific site at the age of 45 years or over are arranged in order of increasing rate of incidence in the population, but the sequence of rates was not drawn to scale. It can be seen at a glance that in neither of the two sexes is there any indication of a relationship between incidence of a particular type of cancer in the population and the chance of its victims dying at ages beyond the reproductive period. The sites with an incidence rate of less than 1.0 (of which there are 8 among the males and 13 among the females) appear to be distributed randomly with regard to the relative mortality above or below the age of 45 years. Conversely, the same seems to hold if those sites in which death from cancer occurred at the earliest average ages (less than 80% of the mortality falling at age 45 or over) are scrutinized with reference to incidence rate. As one particularly striking example, it may be pointed out that cancer of the lip in females was the second lowest among all sites in incidence rate, but the highest in percentage of deaths at 45 years or above. The group of malignant bone tumors, the great majority of which are sarcomas, is by no means among the least common sites. The rate of mortality from bone tumors falls, in fact, in both sexes near the center of the incidence range for specific sites. Mean or median age at death from malignant bone tumors is relatively

early, but not nearly as early as in the case of some other sites (leukemia, brain, testes).

TABLE 1 DATA RELATING TO CANCER MORTALITY AMONG WHITE MALES OF THE UNITED STATES DURING THE YEARS 1941–1945.

SITE	INTERNATIONAL LIST NO.	DEATHS 1941–1945[1]	DEATHS AT AGE 45 YEARS AND OVER WITH STANDARD ERRORS %	ANNUAL DEATH RATE PER 100,000 OF WHITE MALE POPULATION[2]
Buccal cavity and pharynx	45	20,009	95.3 ± 0.17	6.49
Lip	45 a	2,819	96.1 ± 0.37	0.91
Tongue	45 b	4,715	96.5 ± 0.27	1.53
Mouth	45 c	2,628	96.3 ± 0.37	0.85
Jaw bones	45 d	3,219	94.5 ± 0.41	1.04
Pharynx	45 f	6,349	93.9 ± 0.31	2.06
Digestive organs and peritoneum	46	194,666	94.8 ± 0.05	63.11
Esophagus	46 a	10,526	97.4 ± 0.16	3.41
Stomach	46 b	73,182	96.0 ± 0.08	23.73
Duodenum	46 c	1,064	94.5 ± 0.72	0.35
Rectum and anus	46 d	24,672	94.5 ± 0.15	8.00
Intestines (except duodenum and rectum)	46 e	43,372	93.5 ± 0.12	14.06
Liver and biliary passages	46 f	21,724	95.0 ± 0.16	7.04
Pancreas	46 g	16,089	94.3 ± 0.20	5.21
Mesentery and peritoneum	46 h	2,559	74.2 ± 0.88	0.83
Respiratory system	47	43,460	91.2 ± 0.15	14.09
Larynx	47 a	6,650	96.2 ± 0.24	2.16
Trachea, bronchus, mediastinum and unspecified sites	47 b, c, f	12,251	89.5 ± 0.29	3.97
Lung	47 d	24,228	90.8 ± 0.18	7.85
Pleura	47 e	331	82.2 ± 2.10	0.11
Breast	50	997	91.4 ± 0.89	0.32
Genital organs	51	47,480	95.5 ± 0.09	15.40
Scrotum, testes, penis and unspecified sites	51 a, c, d, e	4,126	54.3 ± 0.78	1.34
Prostate	51 b	43,354	99.4 ± 0.03	14.06
Urinary organs	52	37,309	92.8 ± 0.14	12.09
Kidney	52 a	7,422	85.0 ± 0.41	2.41
Bladder	52 b	16,393	97.3 ± 0.14	5.31
Skin (except scrotum)	53	10,068	92.9 ± 0.26	3.27
Central nervous system	54	7,732	55.4 ± 0.57	2.51
Adrenal[3]	55 a	83	72.3 ± 4.93	0.14
Bones (except jaw bones and accessory sinuses)[2]	55 b	980	69.3 ± 1.48	1.62
Thyroid[3]	55 c	198	91.4 ± 1.98	0.33
Leukemia	74	15,632	60.0 ± 0.43	5.07

[1] Exclusive of cases in which age at death was unknown.

[2] Based on all reported deaths, i.e. including those with unknown age. The white male population as of July 1, 1943 was 61,382,831.

[3] Data only for 1942. The white male population as of July 1, 1942 was 60,622,126.

The relationship between percentage of incidence at 45 or more years and the general rate per 100,000 in the population was studied in some detail by finding the regression of the former on the latter. The values considered were

those of the last two columns in tables 1 and 2, with, of course, the broad groups (International List numbers 45, 46, 47, 49, 51 and 52) excluded in

TABLE 2 DATA RELATING TO CANCER MORTALITY AMONG WHITE FEMALES OF THE UNITED STATES DURING THE YEARS 1941–1945.

SITE	INTERNATIONAL LIST NO.	DEATHS 1941–1945[1]	DEATHS AT AGE 45 YEARS AND OVER WITH STANDARD ERRORS %	ANNUAL DEATH RATE PER 100,000 OF WHITE FEMALE POPULATION[2]
Buccal cavity and pharynx	45	4,804	91.5 ± 0.39	1.57
Lip	45 a	263	97.0 ± 1.06	0.086
Tongue	45 b	1,019	93.8 ± 0.76	0.33
Mouth	45 c	765	93.7 ± 0.94	0.25
Jaw bones	45 d	1,010	91.9 ± 0.87	0.33
Pharynx	45 f	1,672	88.0 ± 0.80	0.55
Digestive organs and peritoneum	46	164,834	94.0 ± 0.07	53.79
Esophagus	46 a	2,840	95.9 ± 0.38	0.93
Stomach	46 b	46,006	95.5 ± 0.09	15.01
Duodenum	46 c	823	94.2 ± 0.82	0.27
Rectum and anus	46 d	18,523	92.1 ± 0.25	6.05
Intestines (except duodenum and rectum)	46 e	51,461	92.9 ± 0.11	16.79
Liver and biliary passages	46 f	28,454	94.6 ± 0.14	9.29
Pancreas	46 g	12,333	95.3 ± 0.20	4.02
Mesentery and peritoneum	46 h	2,742	84.6 ± 0.69	0.89
Respiratory system	47	12,859	87.8 ± 0.31	4.19
Larynx	47 a	764	91.4 ± 1.02	0.25
Trachea, bronchus, mediastinum and unspecified sites	47 b, c, f	2,621	85.2 ± 0.70	0.85
Lung	47 d	9,274	88.4 ± 0.34	3.03
Pleura	47 e	200	82.0 ± 2.72	0.065
Uterus	48	72,105	81.6 ± 0.15	23.53
Female genital organs (other than uterus)	49	22,883	83.5 ± 0.27	7.47
Ovary, fallopian tube and parametrium	49 a, b	19,628	82.1 ± 0.28	6.40
Breast	50	74,920	86.8 ± 0.13	24.45
Urinary organs	52	13,325	91.6 ± 0.26	4.35
Kidney	52 a	4,780	82.5 ± 0.55	1.56
Bladder	52 b	8,253	96.8 ± 0.20	2.69
Skin (except vulva)	53	6,205	92.2 ± 0.36	2.03
Central nervous system	54	5,083	51.9 ± 0.71	1.66
Adrenal[3]	55 a	53	58.5 ± 6.80	0.088
Bones (except jaw bones and accessory sinuses)[3]	55 b	866	76.9 ± 1.43	1.44
Thyroid[3]	55 c	408	92.2 ± 1.34	0.68
Leukemia	74	11,506	58.1 ± 0.47	3.75

[1] Exclusive of cases in which age at death was unknown.

[2] Based on all reported deaths, i.e. including those with unknown age. The white female population as of July 1, 1943 was 61,017,824.

[3] Data only for 1942. The white female population as of July 1, 1942 was 60,178,715.

favor of their subdivisions. Thus there were a net 28 sites included in the calculations for each sex. As a modification, that is perhaps preferable, the regression of incidence against the *logarithm* of rate was also calculated. The

usual technique of fitting a straight line by the method of least squares was employed. For both sexes the line sloped slightly upward, i.e., the fraction of deaths occurring among the elderly increased with general incidence in the population. This was true whether rate or logarithm of rate was involved. In no case, however, was the regression or slope statistically significant.[2] We must, accordingly, conclude that there is no dependence of percentage incidence at 45 or more years of age on the rate per 100,000 in the population.

Data published by Gover (1941) offered another opportunity to test the possible existence of a relationship between relative frequency of various types of cancer and mortality at particular ages. Gover gives for the United States, exclusive of Texas, and for the years 1930 through 1932 the mean age at death from cancer of specific sites. Her tables provide these data separately for males and females, for whites and nonwhites. She lists 23 different sites for males and 24 for females. In addition, her tables include for each site the incidence rate adjusted to the age distribution of the total United States population as enumerated in the census of 1930. We have used Gover's data for the white population to determine the coefficients of correlation between rate of incidence and mean age at death. The coefficients thus obtained amount to $+.087$ for the males and to $-.039$ for the females. This is another expression of the complete lack, in our material, of an effect of cancer incidence in particular sites on age at death, such as one might have expected to find if selection had been effective.

COMMENT

Data on cancer mortality, such as we have used here, have many imperfections. Reliability of diagnosis, especially as it relates to determination of the primary site of cancer, frequently leaves much to be desired. There are variations with geographical distribution, degree of urbanization, and probably still other factors. Our basic data are, however, presumably as reliable as any available from other sources and, in any event, it is only upon such material that studies on the possible role of selection can, at present, be based. It should also be kept in mind that the relative frequency of the different primary sites of cancer varies with the age composition of the population and that, consequently, the details of our distributions apply only to the material in hand. Finally, the quantitative differences in volume of the various sites may have an effect on incidence rate, but the extent of this effect can not as yet be estimated.

With these stipulations made, it must still be concluded from our analysis that there is no indication, whatever, for an effect of selection on age incidence

[2] The significance of the regression was tested by finding the reduction in the sum of residuals squared. For neither sex was the reduction near significance. The results were practically unchanged by using the logarithm of rate.

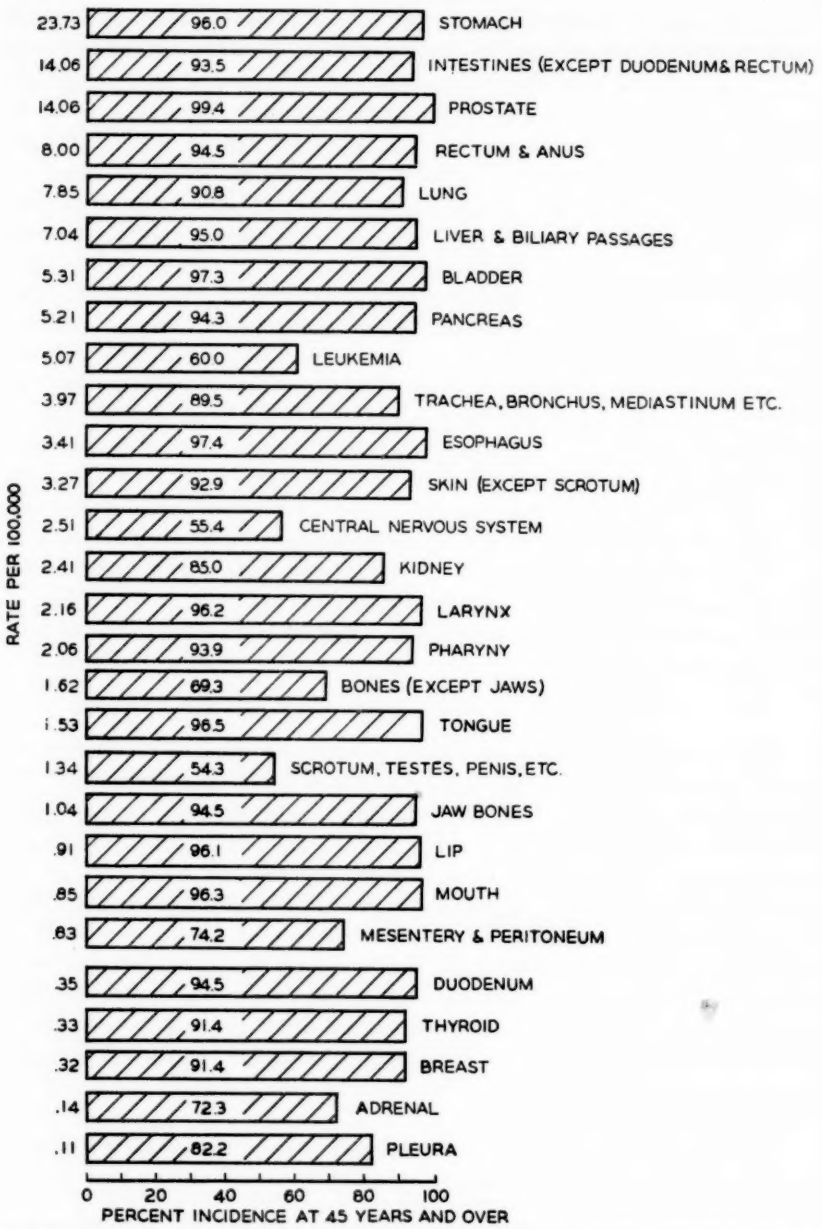
RATE PER 100,000
23.73 96.0 STOMACH
14.06 93.5 INTESTINES (EXCEPT DUODENUM & RECTUM)
14.06 99.4 PROSTATE
8.00 94.5 RECTUM & ANUS
7.85 90.8 LUNG
7.04 95.0 LIVER & BILIARY PASSAGES
5.31 97.3 BLADDER
5.21 94.3 PANCREAS
5.07 60.0 LEUKEMIA
3.97 89.5 TRACHEA, BRONCHUS, MEDIASTINUM ETC.
3.41 97.4 ESOPHAGUS
3.27 92.9 SKIN (EXCEPT SCROTUM)
2.51 55.4 CENTRAL NERVOUS SYSTEM
2.41 85.0 KIDNEY
2.16 96.2 LARYNX
2.06 93.9 PHARYNY
1.62 69.3 BONES (EXCEPT JAWS)
1.53 96.5 TONGUE
1.34 54.3 SCROTUM, TESTES, PENIS, ETC.
1.04 94.5 JAW BONES
.91 96.1 LIP
.85 96.3 MOUTH
.83 74.2 MESENTERY & PERITONEUM
.35 94.5 DUODENUM
.33 91.4 THYROID
.32 91.4 BREAST
.14 72.3 ADRENAL
.11 82.2 PLEURA
0 20 40 60 80 100
PERCENT INCIDENCE AT 45 YEARS AND OVER

FIGURE 1. Cancer deaths at ages of 45 years and over in percent of mortality at all ages. Sites arranged according to incidence in population. Data for white males in the United States, 1941 through 1945.

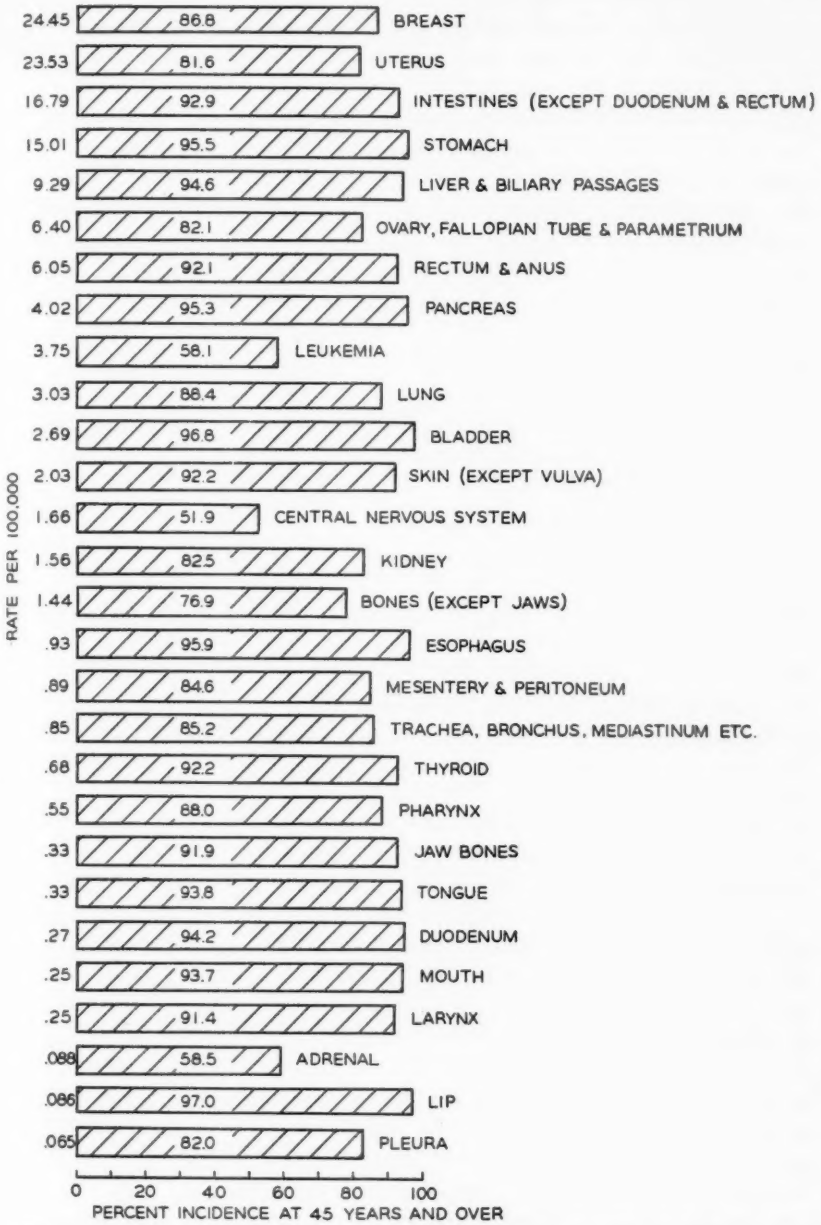
RATE PER 100,000
24.45 86.8 BREAST
23.53 81.6 UTERUS
16.79 92.9 INTESTINES (EXCEPT DUODENUM & RECTUM)
15.01 95.5 STOMACH
9.29 94.6 LIVER & BILIARY PASSAGES
6.40 82.1 OVARY, FALLOPIAN TUBE & PARAMETRIUM
6.05 92.1 RECTUM & ANUS
4.02 95.3 PANCREAS
3.75 58.1 LEUKEMIA
3.03 88.4 LUNG
2.69 96.8 BLADDER
2.03 92.2 SKIN (EXCEPT VULVA)
1.66 51.9 CENTRAL NERVOUS SYSTEM
1.56 82.5 KIDNEY
1.44 76.9 BONES (EXCEPT JAWS)
.93 95.9 ESOPHAGUS
.89 84.6 MESENTERY & PERITONEUM
.85 85.2 TRACHEA, BRONCHUS, MEDIASTINUM ETC.
.68 92.2 THYROID
.55 88.0 PHARYNX
.33 91.9 JAW BONES
.33 93.8 TONGUE
.27 94.2 DUODENUM
.25 93.7 MOUTH
.25 91.4 LARYNX
.088 58.5 ADRENAL
.086 97.0 LIP
.065 82.0 PLEURA
0 20 40 60 80 100
PERCENT INCIDENCE AT 45 YEARS AND OVER

FIGURE 2. Cancer deaths at ages of 45 years and over in percent of mortality at all ages. Sites arranged according to incidence in population. Data for white females in the United States, 1941 through 1945.

of particular types of cancer. Such differences in age distribution at death as exist between different sites must presumably be explained on the basis of factors inherent in the sites themselves. One might be inclined to single out some sites, especially the target organs of certain endocrine glands, for special consideration because of endocrine imbalances occurring at the end of the reproductive period. We believe, however, that in the present stage of knowledge the characteristic age distributions of cancer mortality may be interpreted quite generally as a consequence of differential tissue ageing (in the broadest sense and referring to structure as well as function) in the various sites with attendant metabolic dislocations within and among organs.

A good illustration of the role which structural peculiarities of tissues play in the incidence of cancer emerges from a comparison of the death rates due to cancer of the skin in the white and nonwhite population groups of the United States. For reasons of the reliability of available data we have limited our general analysis to the white group, but in the case of skin cancer a comparison seems quite justified.

It is well established that the incidence of and mortality from cancer of the skin is considerably lower among Negroes than among white people (Holmes, 1928; Gover, 1941; Dorn, 1944), and it has been shown that this holds true even after allowance has been made for the different age compositions of the two groups. These differences between whites and nonwhites are, and in a similar manner, found among males and females. The observations of Gover (1941) show, however, that up to the age of about 40 years in males and 50 years in females, i.e., to about the end of the reproductive period, the rates of mortality from skin cancer are very similar among whites and nonwhites. It is only after these ages that in the nonwhites the mortality rates from this cause do not follow the continuing mortality rate increase of the whites. There can be little doubt that the causes of reduced skin cancer mortality among the nonwhite population are related to skin pigmentation and superior adaptation afforded by it. It seems reasonable to assume that the protection furnished by pigmentation finds its principal expression in a lessening of those ageing factors which among whites are presumably responsible for the relatively great toll taken by skin cancer mortality in advanced years of life. In any event, these data would seem to provide as little support for an explanation of age-incidence differences in terms of selection as did our analysis of mortality from cancer of different sites in the white population. This is not to deny, of course, that in other situations selection may play an important role in determining age of onset of certain human diseases and age at death. Instances of this kind have been pointed out by Haldane (1942).

In an interesting publication Denoix and Moine (1951) recently reported the rate of death from cancer in various countries. They gave such data (in their tables VI and VII) for 1936 and 1946, tabulated according to sex and

several sites (including sites 45, 46, 47 and 50). Their observations confirm impressively the existence of temporal trends as well as of geographic differences in incidence. Yet, if one studies their tabulations with reference to age at death, a comparison of rare and relatively common sites (e.g., male vs. female breast or buccal cavity vs. digestive organs) reveals no evidence suggestive of changes in age incidence such as might have been brought on by selection. This is equally true for comparisons within or between countries and within the same or between different years.

SUMMARY

An analysis of data for mortality from cancer of specific sites among males and females of the white population of the United States for the years 1941 through 1945 gave no evidence for an effect of selection on age at death. There was no correlation between incidence rate of different types of cancer and mean age at death (data for 1930 through 1932). The differences in age incidence of cancer mortality existing between various sites are presumably due to factors associated with "differential ageing" of tissues and organs.

ACKNOWLEDGMENTS

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Linkage Tests of Mediterranean Anemia with Blood Groups, Blood Types, Rh Factors and Eye Color

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INTRODUCTION

MEDITERRANEAN ANEMIA is a hypochromic, iron-refractory anemia prevalent among, though not exclusive to, people living in or originating from the eastern basin of the Mediterranean Sea. It ranges from a very mild type of anemia recognizable only through minor hematologic changes to a serious condition with usually fatal outlook before puberty. An unusual degree of erythrocytic thinness (leptocytosis) in association with other red cell abnormalities, such as elliptocytosis and increased hypotonic resistance, are common denominators seen in all the types, whether mild or severe.

Cooley et al. (1925) were the first to describe the most severe cases, separating them from the rather confusing group of blood disorders then known as Von Jaksch's Anemia. These severe cases have since been known as "Cooley's Anemia." The condition manifests itself within the first year of life or shortly afterwards. The patients are markedly pale and slightly icteric, with a peculiar configuration of the facial bones often resulting in a mongoloid appearance. The spleen and liver are enlarged to a variable extent. Study of the blood shows hypochromic microcytic anemias, with many red blood cell abnormalities including the presence of numerous target cells, oval cells, stippled cells, microcytes and occasional polychromatophilic macrocytes. Schistocytes, elliptical red cells, and nucleated red blood cells are commonly found. The hypotonic fragility of the red blood cells is constantly decreased. X-rays of bones show striking osteoporitic changes.

In 1940 and, since then, milder cases showing similar though less marked laboratory abnormalities were recognized (Dameshek, 1940, 1942) (Wintrobe et al., 1940) (Strauss, Daland and Fox, 1941). The mildest of these cases showed only changes in erythrocyte morphology and increased hypotonic resistance. Cases of intermediate degree of severity were also recognized, enabling the establishment of a continuous series of cases with differing degrees of severity ranging from the mildest to the most severe. It should be appreciated that cases of the mild form of Cooley's Anemia, surviving into adult life, were reported several years ago, usually by Italian and Greek investigators (Stillman, 1917) (Angelini, 1937) (Caminopetros, 1938).

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Dameshek (1942) divided his cases into several groups which he defined according to the outstanding clinical and laboratory findings. Valentine and Neel (1944, 1945) discriminated only two types: Thalassemia major and Thalassemia minor, and stated, "Thalassemia major is in most essential respects an exaggeration of the "Thalassemia minor" and "the chief well established qualitative difference is the appearance in Thalassemia major of circulating erythroblasts."

Various names have been proposed for this disease, such as: Erythroblastic Anemia (Cooley and Lee, 1925), Cooley's Anemia (Daland and Strauss, 1948), Cooley's Trait (Ibid.), Thalassemia (Valentine and Neel, 1944) and Mediterranean Anemia (Dameshek, 1942). The lack of a generally accepted nomenclature is probably due to the unsatisfactory nature of those proposed.

The present pathogenic explanation of the disease is that it consists of an inherent metabolic defect of hemoglobin production and of erythrocyte formation. This results in a reduction in hemoglobin and in leptocytosis. The increased fecal urobilinogen output in cases of moderate and marked severity indicates an increase in red blood cell destruction.

One of the earliest papers dealing with the familial and hereditary aspects of this disease was that of Angelini (1937). He studied twenty-six members of six families and found that nearly all parents and siblings showed a marked increase in red blood cell resistance to hemolysis. Caminopetros (1938) believed that Mediterranean Anemia represented a constitutional hereditary mutation of the erythropoietic parenchyma. He reported that examination of the fragility of the red blood cells constituted a reliable method for the detection of apparently normal carriers of the disease. He also investigated the possibility of linkage between the blood groups and the morbid hereditary elements. Comparison of the blood groups of the affected and the normal members of the family showed that there was no agreement between the disease and a given blood group but, "There is identity of blood group between parents transmitting the disease and their descendants who receive it." This statement has never been confirmed.

Three different theories have been advanced to explain the transmission of Mediterranean Anemia. One holds that both mild and severe conditions are due to a dominant gene which varies greatly in expression (Smith, 1943). A different concept of the hereditary transmission explains the severe anemia as being due to the interaction of two non-allelic dominant factors (McIntosh and Wood, 1942). The third and simplest of these theories (Dameshek, 1942) holds that the severe disease is present in individuals homozygous for the transmissible factor while the mild form of the disease is seen in heterozygous individuals.

Papers by Wolman and Dickstein (1946), Neel and Valentine (1947), Daland and Strauss (1948), and Heinle and Read (1948) have presented new families

with data showing the method of transmission. These studies agree that the transmission of the disease and its "carrier" state can be explained on the basis that mild Mediterranean Anemia is caused by the effects of a single incompletely dominant gene whose effects are recognizable in the heterozygote

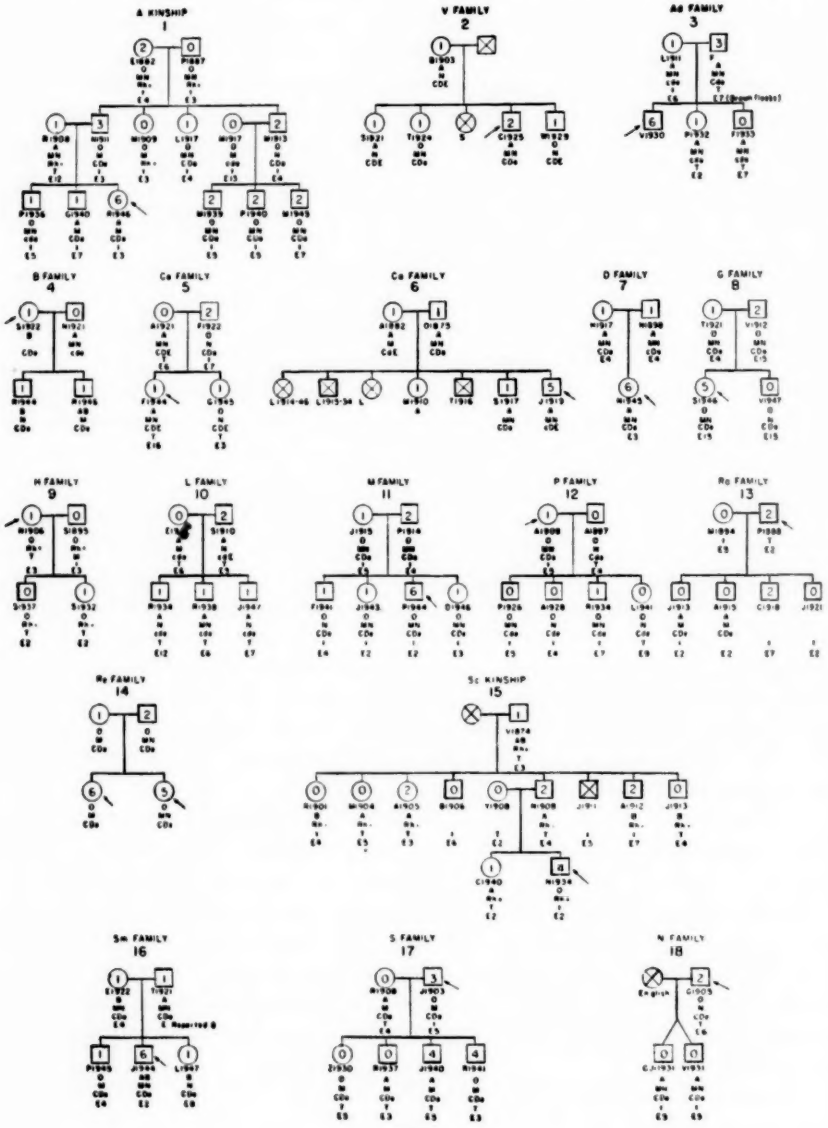

FIG. 1

by hematologic examination and fragility tests of the blood. An individual homozygous for the hereditary factor for Mediterranean Anemia would exhibit the severe form of the disease and usually would not survive adolescence.

MATERIAL AND METHOD

The cases on which the data of this study are based came to our attention because one member of each family sought medical advice either for the severe erythroblastic ("Cooley's") form of the disease or for the milder "target oval cell jaundice." A few of the latter cases were recognized while under investigation for an unrelated disorder. When the diagnosis of Mediterranean Anemia in any form or of any degree was made on a patient, all available and cooperative members of the family were called in. Complete history, as well as physical examination and blood counts were taken routinely. Other investigations included hematocrit determination, bilirubin, hypotonic fragility, and in many cases X-rays of bones, fecal urobilinogen, serum iron, etc.

Nineteen kinships were accepted as offering data complete enough to be useful for our study. The kinships were largely of Mediterranean origin. Those kinships (fig. 1) shown in pedigrees 1, 3, 5, 6, 8, and 10–17 were of Italian descent both on maternal and paternal sides. The subjects of pedigrees 2 and 7 were of Greek origin. Family 9 was of Armenian descent. In family 4 the father was of French-Canadian descent and the mother of Italian origin. In family 18 the father was of Italian descent while the mother was of English origin.

FIG. 1. Numbers enclosed within the squares (representing males) or the circles (representing females) refer to the severity of the disease (M.A) in accordance with table I. The data below each square or circle have the following meanings: The first item gives the first initials of the individual and the year of his or her birth. This is followed by symbols for blood group; blood type; Rh factors, taster or non-taster, and eye color classified according to the eye color scale of Martin. Where information for these characters was not available, the space has been left blank. The meanings of the symbols and abbreviations are as follows:

○	Female
□	Male
⊗	Not Examined
/	Proband
1	Male with M.A. of type I
G1940	Initial of first name followed by year of birth
AB	Blood group
M	Blood type
CDe	Rh factors, tested with C, D and E anti-sera cells agglutinated only by C and D anti-sera
T	Taster of Phenyl-thio-carbamide t-non taster
E7	Eye color according to Martin's eye color standard

TABLE 1. CLASSIFICATION OF DEGREES OF SEVERITY OF MEDITERRANEAN ANEMIA

	GROUP*	R.B.C. (M)	HEMOGLOBIN*	TARGET, OVAL, STIPPLE CELLS	MICRO, POIKILOCYTES	HYPOTONIC FRAGILITY DEGREE OF RESISTANCE	SPLENOMEGALY	JAUNDICE	BONE CHANGES	NUCLEATED R.B.C.'s
NORMAL	0	4.5–5.5	14–16g 90–103%	0	0	0	0	0	0	0
Congenital lepto- and elliptocytosis with or without mild hypochromic anemia	1	4.5–5.5	10.1–14g 65–90%	+	±	++	0	0	0	0
Hypochromic Erythrocytosis	2	6–8	12.5g + 80%	+	−	++	0	0	0	0
Hypochromic Erythrocytosis with Splenomegaly and jaundice	3	5.5–6.5	10.1–12.5g 65–80%	+	±	+++	+	+	0	0
Congenital Hemolytic target, oval cell, jaundice	4	3.0–4.5	7.8–10.1g 50–65%	++	±	+++	++	+	+	0
Adult Anerythroblastic Type of Cooley's Anemia	5	2.0–3.0	7.8g 50%	++	±	++++	+++	++	++	Usually + Occasionally −
Cooley's Erythroblastic Anemia	6	1.5–2	6.2g 40%	++	±	++++	++++	+++	++++	+++

* Groups 1 and 2 represent a mild form, 3 and 4 a moderate form, and 5 and 6 the severe form of Mediterranean Anemia.

The subjects available for study were subdivided according to the symptoms present and to an overall evaluation of the type and degree of severity of the disease. For this purpose, a classification (table 1) which was based on Dameshek's (1942) earlier work was used. This classification does not attempt to separate clearcut autonomous disease entities, but establishes the varying intensity of symptoms and findings as they appear in the same pathologic process. It is intended merely as a working guide and can be modified to include fewer or more groups. Transitional cases are found which could fit in one group according to some findings and in another group according to others.

Groups 1 and 2 represent the disease in its mildest manifestations with very slight reduction of hemoglobin (normal red blood cell count in group 1 or increased red blood cell count in group 2) and slight morphologic changes of the red blood cells. Groups 3 and 4 represent the intermediate and moderately severe types of the disease. The anemia is intermediate in severity. Slight jaundice and splenomegaly are usually present; no nucleated red cells or bone changes are seen.

These two groups are differentiated by the presence of erythrocytosis in group 3 and by its absence in group 4. Patients in groups 5 and 6 present the most severe types of the disease. Group 6 includes the cases originally described by Cooley as erythroblastic anemia; the principal difference between the two groups being the degree of anemia, which is extremely severe in group 6. Nucleated red blood cells are practically always found in group 6 and are usually present in group 5, although an occasional nucleated red blood cell may be seen, even in the mildest of these cases if a sufficient number of blood films are examined.

The objects of the genetic portion of this study were twofold:—first, to trace the method of transmission of Mediterranean Anemia in the families studied—and second, to determine whether linkage exists between Mediterranean Anemia and other known genes. The inherited characters selected for the purposes of this study were:—blood groups ABO, blood types MN, Rh factors C, D, and E, ability to taste phenyl-thio-carbamide, and blue eye color.

The four blood groups A, B, AB and O are the results of three alleles, namely, I^A, I^B, and I^O which occupy a particular locus on one of the autosomes. I^A shows no dominance over I^B, while either I^A and I^B are completely dominant to I^O. Standard blood grouping procedure was used. The three blood types in man—M, N, MN –result from the effects of two alleles Ag^M and Ag^N, whose locus is also on one of the autosomes, but not on the same autosome as the one which contains the locus of the ABO genes. Ag^M and Ag^N alleles show no dominance with regard to each other. A person genetically Ag^MAg^N is type MN.

Three anti-sera were used to determine the Rh factors present. These were anti-D (anti-Rh_0); anti-C (anti-rh'); and anti-E (anti-rh''). Tube agglutination tests were performed according to Wiener's technique.

Two systems of nomenclature are at present used to denote the Rh factors (Castle et al., 1948). These are the Fisher-Race (Mollison, Mourant and Race, 1948) and Wiener (1946) systems. The primary difference between the two systems other than symbols and nomenclature is that the Fisher-Race theory maintains that the inheritance of the Rh factors can best be explained by assuming the existence of three different but closely linked loci, while the Wiener system maintains that multiple alleles exist at a single locus. For purposes of this paper the C, D, E notation will be used. Since no tests were made for c, d, and e antigens in this study, the genes for C, D, and E are assumed to be, insofar as these data are concerned, completely dominant to those for c, d, and e. In other words, an EE individual was not differentiated by our methods from an Ee individual. In several of the pedigrees, individuals are represented as either Rh positive or Rh negative. Such individuals were tested early in this study with the use of only anti-D serum and are therefore indicated only as Rh positive or Rh negative. In all other cases the antigens C, D or E, when present, were recorded in the pedigree.

The ability to taste phenyl-thio-carbamide (Blakeslee, 1932) (Falconer, 1947) is an inherited character in humans attributed to the effects of a single autosomal gene *T* which is completely dominant to its allele *t*. The letter T in a pedigree refers to the ability of the individual to taste phenyl-thio-carbamide, while t represents a non-taster. Early in this study this character was tested for by the use of paper treated with the chemical phenyl-thio-carbamide. The paper proved extremely variable, due either to uneven treatment or deterioration. Subsequently, a few crystals of phenyl-thio-carbamide were placed on the tongue of the person being tested. This revised method proved to be more satisfactory.

Eye color was classified by the Augenfarben Tafel of Martin[1] (1928), which consists of sixteen glass eyes ranging from fully pigmented E-1 to very light blue, E-16. Whenever possible, eye color was matched by daylight. The category of eye color most closely matching the eye color of an individual is given as the last item beneath the figure representing that person. In the pedigrees this is shown by values ranging from E-2 to E-16. Blue eye color is inherited as a simple recessive character which is not known to be linked to any of the other inherited characters included in this study. Eye colors from E-1 up to and including E-8 are considered "brown," while categories E-9 to E-16 are considered "blue."

Details pertaining to one of our more extensive pedigrees are as follows: The family came to our attention through R. A. who was first seen in August, 1946, at the age of six months. Chief complaints consisted of pallor, poor feeding habits, and deficiency in the normal weight gain. Physical examina-

[1] Made available by the Harvard Museum of Comparative Anthropology.

tions revealed a well developed and well nourished, pale "waxy" appearing female in no acute distress. Ears, nose, throat, neck, and cardiovascular system, negative. The abdomen was somewhat protuberant and soft. The liver was palpable one finger below the right costal margin; the spleen was felt 1½ fingers below the left costal margin. The extremities and genitalia were normal. Blood counts: RBC 3.03, Hgb. 5.3 gms. 34%, WBC 11.700, the differential white blood cell count—adult polymorphs 16%, lymphocytes 75%, monocytes 1%, eosinophiles 4%. Four normoblasts C were seen in counting 100 white cells. The red blood cells showed marked anisocytosis and poikilocytosis; target

TABLE 2. DETAILED FINDINGS IN FAMILY 1

PEDIGREE LOCATION	R.B.C. (1)	HEMOGLOBIN (2)	TARGET CELLS (3)	OVAL CELLS (3)	SPLEEN SIZE	BILIRUBIN (4)	BONE CHANGES (5)
III-3*	3.0	5.3	11.2	.2	+++	1.2–2.5	pos.
I-1	6.1	11.0	0.3	4.5	0	0.2	neg.
I-2	4.4	12.9	0	0	0		neg.
II-1	4.7	10.7	9.0	3.4	0	0.5	neg.
II-2	6.1	11.7	2.3	1.8	+	1.0	neg.
II-3	4.6	12.1	0	0	0		neg.
II-4	4.9	12.5	0	0	0	0.6	
II-5	4.2	12.9	0	0	0		
II-6	5.8	12.9	1.4	3.0	0		
III-1	4.7	10.7	5.4	2.0	0	0.5	neg.
III-2	4.2	10.1	5.3	2.4	0	0.2	neg.
III-4	6.2	10.1	6.2	2.6	0		
III-5	6.4	10.4	6.0	4.0	+		
III-6	4.7	10.4	0.2	1.4	0		

* Propositus.
(1) millions per cubic centimeter.
(2) grams per 100 cubic centimeters.
(3) per 100 red blood cells.
(4) milligrams per 100 cubic centimeters of serum.
(5) by X-ray of hands.

cells were 1.4%, oval cells, 9.4%. Since that time the child has been followed at regular intervals. The lowest values of red cell count and hemoglobin value have been 1.5 M. and 3.9 grams (25%), respectively. The red cells showed greatly increased resistance to hypotonic salt solutions.

The fecal urobilinogen was always high. It was between 38 and 100 mg/day. (Normal value for the patient's age, weight, and hemoglobin level is about 10–15 mg/day.) X-rays of bones revealed evidence of osteoporosis and loss of the fine trabeculae, particularly of the pelvis, the posterior ends of the ribs, the small bones of the hands, and the lower jaw.

The mother's family was of Sicilian extraction. The father's family was originally from Southeastern Italy. The family history was entirely negative. Parents, two siblings, one paternal uncle, two paternal aunts, paternal grand-

parents, maternal uncles, maternal aunts and cousins were living and well. There were no deaths of siblings, uncles or aunts or cousins. Maternal grandfather had died, aged 63, of pneumonia; maternal grandmother had also died, aged 72, of "dropsy." Despite the negative history, as many members of the family as could be reached were questioned and examined with regard to pallor, jaundice, and splenomegaly. Complete blood counts were taken in all cases, and in a few instances fecal urobilinogen excretions were determined. X-rays and hypotonic fragility tests were done in most instances. The significant data on the relatives are given in table 2.

Only one subject was classified in group 6 (table 1), this being the patient described above. One patient was classified in group 3 because of the high red blood cell count, the increased bilirubin value and the splenomegaly. Five subjects were classified in group 2 and three in group 1. The hemoglobin value in these two groups was similar, but the counts were high in one group and normal to slightly reduced in the other. Patients classified in groups 1 and 2 had normal sized spleens and normal bilirubin values. Bone changes by X-ray and nucleated red blood cells in the peripheral blood vessels were found only in the most severely afflicted patients.

DISCUSSION

The earliest age at which symptoms of severe Mediterranean Anemia have been seen in this laboratory has been six months. Earlier hematologic symptoms may be present but have not been observed, probably because of lack of examination of the blood of newborn infants with this disease in mind.

One of the objects of the present study was to investigate the transmission of Mediterranean Anemia. Previous studies have indicated that transmission can be adequately explained on the basis of an incompletely dominant gene. The data of this study confirm this and show no significant deviation from expected ratios. In every case of severe anemia, both parents evidenced the mild disorder.

Since genes are located on or as part of chromosomes, gene transmission cannot be separated from chromosome transmission. This intimate relationship between genes and chromosomes gives rise to the condition referred to genetically as "linkage." From a medical standpoint, linked transmission is of interest because it offers the possibility of predicting inherited characters before they become manifest. Such prediction might be made with high accuracy in certain cases if two genes (one being the morbid hereditary factor) were known to be closely linked. Mediterranean Anemia can, however, be detected by blood examination so that, for this disease, linkage at present would offer little additional information.

For an inherited character to be useful in linkage studies, it must have certain features:—simple hereditary transmission, be capable of recognition by

visual examination of the individual or by simple (or at least available) tests, and have a high incidence in the population studied. The inherited characters chosen for study are believed to approximate these conditions.

Finney's method (1940) for the detection of linkage in humans is a method of statistical treatment of pedigree information in order to test for the presence (not degree) of linkage between heritable characters. Use of this method demands that the mode of heredity of the characters studied is known, that crossover and non-crossover gametes are recognizable in the offspring and that members of a family are ascertained for the characters concerned. A knowledge of the frequency of the genes responsible for the characters being studied in that population may be used to evaluate members of a family not available for examination.

TABLE 3. SUMMARY OF LINKAGE TESTS

LINKAGE TESTED BETWEEN	NUMBER OF FAMILIES	TOTAL NUMBER OF CHILDREN	INDICATION OF LINKAGE BY FINNEY METHOD
ABO and M.A.	2	6	none
MN and M.A.	8	18	none
Rh and M.A.	3	8	none
T and M.A.	4	15	none
Blue eye color and M.A.	2	5	none

Innate difficulties of linkage studies, other than those usually encountered in gathering family data, involve the fact that the number of linkage groups cannot exceed the chromosome number of the species. It follows, therefore, that the chance of finding linkage between any two loci selected at random is small. To this difficulty may be added the consideration that only a small portion of the data gathered can be used for linkage tests. Since only families in which at least one parent is heterozygous for both pairs of genes can furnish information regarding linkage between two loci, severe limitation of data usable for linkage tests usually results. Snyder, Russell and Graham (1947) report only 5 out of 33 families suitable for a test of linkage between the locus for sickle cells and that for the MN blood types.

In this study the number of families suitable for linkage tests was also severely limited, as shown in table 3. No evidence of linkage was obtained. Complete pedigree data are made available in the hope that these data may be useful in other studies.

Though the observed transmission can be well explained by simple Mendelian heredity, this explanation rests on a classification of Mediterranean Anemia into severe, mild, and normal. Such a classification, convenient though it may be genetically, must be interpreted in practice to mean an intergrading series of conditions ranging from normal to severe.

The variations observed clinically in heterozygous individuals are probably caused by several, perhaps many, modifying factors which are also inherited and which affect the expression of the primary gene. Thus, of two individuals, both heterozygous, one may receive modifiers favoring expression of symptoms, while the other may inherit a balance of factors favoring suppression. The limits of symptom suppression are such that a heterozygous individual is never completely normal and rarely approaches the severity of the homozygous form of the disease.

CONCLUSIONS

The transmission of Mediterranean Anemia by an incompletely dominant autosomal gene is supported by the evidence here presented. The severe form of Mediterranean Anemia is attributed to the homozygous condition of the responsible gene, while the milder condition is due to the heterozygous "carrier" state. The varying severity observed is explained as being due to modifying factors (also hereditary) which condition the severity of the disease caused by the primary gene.

Using Finney's method no evidence was found of linkage between Mediterranean Anemia and the blood groups, the blood types, Rh factors, phenyl-thio-carbamide taster, or blue eye color.

The need of studies on very young infants to determine the onset of Mediterranean Anemia is pointed out.

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Frequencies of Consanguineous Marriages in Brazilian Populations

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THE DEVELOPMENT of civilization has transformed mankind from a species consisting of a multitude of small endogamous groups into a species composed of very large and only imperfectly isolated Mendelian populations. As pointed out by many authors, especially by Dahlberg (1929, 1938), Boyd and Boyd (1941), and Neel, Kodani, Brewer and Anderson (1949), this process has a number of very important genetic consequences, one of which is a decrease of the frequency of marriages between relatives. A review of the available data on the frequencies of consanguineous marriages in various European countries and in Japan is contained in the paper of Neel et al. just referred to. The purpose of the present article is to put on record some preliminary data on the frequencies of marriages between relatives in certain Brazilian populations.

MATERIAL

The data at our disposal are derived from parts of only two of the States of which Brazil is composed, namely of São Paulo and Minas Gerais. São Paulo is a coastal state, which is undergoing a rapid process of industrialization and is served by the densest highway and railway net in Brazil. Minas Gerais lies inland, is chiefly agricultural, and possesses a system of communications which is much inferior to that in São Paulo. It also has a purely Brazilian population, in which the frequency of foreign born persons is very much lower than it is in São Paulo with its Italian, Japanese, and German immigrants and their immediate descendants.

In Brazil, both secular and religious laws control the degree of consanguinity which is permissible in marriage. The secular laws, which apply in the entire country, forbid marriages between ancestors and descendants, as well as between siblings. Marriages between uncles and nieces, and between aunts and nephews, require a certification by the medical authorities that the state of health of the parties wishing to contract marriage is not likely to affect adversely their offspring. The Catholic Church requires a special dispensation of the ecclesiastic authorities for marriages between uncles and nieces, aunts and nephews, and between first, second, and third cousins.

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A great majority of the data presented in this article has been obtained by examination of the books of marriage records maintained by the Catholic parishes. A minority of the data have been derived from the official church publications, or from other persons who, in response to the writer's requests, have examined the marriage record books. Since, according to the 1940 census, approximately 95 per cent of the Brazilian populations are Catholics, we are confident that the data reflect accurately the frequencies of consanguineous marriages in the populations analyzed. The older parish books had recorded also degrees of consanguinity lower than the third cousins. Since, however, such remote relationships no longer constitute religious impediments for marriage, the more recent records fail to mention them, and they are ignored in the following tables.

The data for one of the parishes, namely, for Aparecida do Norte, have been broken up further into two parts: those pertaining to the marriages in which at least one of the parties was a resident of the parish, and those between parties resident in other parishes (pilgrims). Aparecida do Norte is a small town with about, 9,000 inhabitants, and its township contains slightly more than 15,000 inhabitants. This town is, however, located in a region of relatively high demographic density, about equidistant from the cities of São Paulo and Rio de Janeiro, and the relatively densely inhabited southern part of Minas Gerais. More important, Aparecida do Norte is the greatest center of Catholic pilgrimage in Brazil; approximately 700 marriages concluded there every year are between parties resident in small towns and villages of the surrounding territory.

It should also be noted that our data show the frequencies of marriages between certain classes of relatives and not the average degrees of consanguinity. From the church records only the data for the greatest degree of consanguinity existing between the bride and the groom are given. The multiple consanguinity is, thus, ignored. The data for the nineteenth century often contain still another flaw, since in many instances marriages are recorded between parties one or both of which had an unknown father and in some cases also an unknown mother. Such a situation occurred especially among the slaves and the freedmen. This difficulty has been obviated by ignoring, in the data for the nineteenth century, all the marriages in which at least one of the parties could not name both parents. This correction does not, however, take care of the possible degrees of consanguinity beyond that of the first cousins. As a result, the frequencies of the consanguineous marriages during the nineteenth century were assuredly somewhat greater than indicated by our figures. During the twentieth century, the numbers of persons who did not know both of their parents proved to be so small that this source of error is no longer of much importance.

THE DATA

Tables 1–6 show the frequencies of marriages between relatives in various populations analyzed. The frequencies of marriages between first cousins in some parishes are summarized in Figure 1. This Figure includes data for two parishes within the city of São Paulo (Santa Efigenia and Freguesia do Ó), for three parishes in the State of São Paulo (Mogi das Cruzes, Itapecerica, and Aparecida do Norte), and between the outsiders who have their marriages consecrated at Aparecida do Norte (the upper curve in fig. 1). It is obvious at

TABLE 1. FREQUENCY, IN PER CENT, OF MARRIAGES BETWEEN RELATIVES IN TWO PARISHES OF THE CITY OF SÃO PAULO

PARISH & TIME	N	UNCLE-NIECE & AUNT-NEPHEW	FIRST COUSINS	SECOND COUSINS	THIRD COUSINS	TOTAL
Santa Efigênia						
1836–1855	238	5.5	5.1	1.7	3.4	15.6
1871–1880	250	0.8	2.0	0.0	1.2	4.0
1886–1888	240	0.8	3.8	0.4	0.4	5.4
1894–1896	232	0.0	2.2	0.4	0.4	3.0
1898–1899	231	0.4	1.7	0.0	0.9	3.0
1900–1905	958	0.0	0.7	0.1	0.3	1.1
1906–1911	953	0.3	1.5	0.8	0.4	3.0
1912–1922	1599	0.2	1.9	0.1	0.2	2.4
1923–1929	1598	0.1	2.2	0.2	0.5	3.1
1930–1938	1606	0.0	0.6	0.1	0.5	1.2
1939–1950	1514	0.0	0.5	0.2	0.1	0.8
Freguesia do Ó						
1804–1850	255	3.9	11.4	2.0	5.9	23.1
1851–1889	266	2.3	11.3	2.6	6.8	22.9
1890–1907	255	0.0	6.7	2.0	2.0	10.6
1908–1920	275	0.4	4.0	0.7	0.7	5.8
1921–1929	326	0.0	2.8	1.2	0.9	4.9
1930–1941	799	0.1	1.0	0.3	0.3	1.6
1942–1950	1142	0.0	0.4	0.0	0.1	0.5

a glance that the lowest frequencies of marriages between relatives are observed in the city of São Paulo, and the greatest in the interior of the country.

Table 7 classifies the data for Mogi das Cruzes, Itapecerica, Parnaiba, Aparecida do Norte, the city of São Paulo, and for Boa Esperança (in the State of Minas Gerais) according to the birth places of the parties to a given marriage. The following classes are distinguished:

WH—the bride and the groom born in the given parish
wH—the bride born outside and the groom within the parish
Wh—the bride born within and the groom outside the parish
wh—both bride and groom born in different parishes and outside the parish in which they marry

wh—both bride and groom born in the same parish but not in the parish in which they marry.

Thus, the classes WH and *wh* are composed of parties both of whom were born in the same parish, and, accordingly, their sum is entered in the column "same parish". In the column "different parishes" are entered the wH, Wh, and wh classes. The rightmost column (Index) gives the ratios of the "differ-

TABLE 2. FREQUENCY, IN PER CENT, OF MARRIAGES BETWEEN RELATIVES IN TWO SUBURBAN PARISHES, IN THE VICINITY OF THE CITY OF SÃO PAULO

PARISH & TIME	N	UNCLE-NIECE & AUNT-NEPHEW	FIRST COUSINS	SECOND COUSINS	THIRD COUSINS	TOTAL
Mogi das Cruzes						
1838–1845	285	1.1	6.7	2.1	3.5	13.3
1846–1850	200	1.5	7.0	5.0	4.5	18.0
1864–1868	277	1.8	7.2	2.2	5.1	16.3
1878–1881	254	0.4	6.7	3.2	2.4	12.6
1882–1885	261	1.5	4.6	0.8	3.4	10.3
1886–1890	368	0.5	6.5	2.4	1.1	10.6
1906–1908	369	0.0	4.6	3.2	4.9	12.7
1909–1911	372	0.5	4.3	1.9	2.7	9.4
1912–1915	381	0.0	4.5	2.4	2.4	9.2
1916–1921	800	0.2	2.9	2.2	1.5	6.9
1922–1927	1199	0.1	2.8	1.4	2.4	6.7
1928–1933	945	0.0	2.3	0.4	1.3	4.0
1940–1946	1415	0.0	1.4	0.7	1.1	3.2
Itapecerica						
1842–1852	185	1.1	10.3	2.7	8.1	22.2
1853–1864	223	0.9	9.9	3.6	7.2	21.5
1881–1887	265	2.6	9.4	0.0	9.4	21.5
1888–1893	208	2.9	9.1	1.0	3.4	16.4
1894–1899	280	0.7	8.2	0.0	2.5	11.4
1900–1907	369	1.4	5.7	0.8	1.1	8.9
1908–1911	315	0.0	4.4	0.9	0.9	6.3
1912–1917	318	0.3	3.1	0.9	1.3	5.7
1918–1925	596	0.2	6.2	0.3	0.5	7.2
1926–1930	516	0.4	3.3	0.8	1.4	5.8
1931–1936	480	0.2	2.1	0.6	0.4	3.3
1939–1944	532	0.0	5.3	1.5	0.9	7.7

ent" and the "same". High indices (above 7) have been obtained only in the city of São Paulo. Low indices are characteristic of the small parishes in the interior of the country.

ANALYSIS OF THE DATA

It is convenient to begin the analysis of the data with a consideration of the two parishes of the city of São Paulo, namely, Santa Efigenia and Freguesia do Ó. The former is located near the center of the city in a region now

characterized by intense business activity. The latter is suburban and is located on a hill the access to which was rather difficult during the last century, and which is, in fact, rather isolated from the city proper even at present.

TABLE 3. FREQUENCY, IN PER CENT, OF MARRIAGES BETWEEN RELATIVES IN SOME PARISHES IN THE STATE OF SÃO PAULO

PARISH & TIME	N	UNCLE-NIECE & AUNT-NEPHEW	FIRST COUSINS	SECOND COUSINS	THIRD COUSINS	TOTAL
Cotia						
1838–1851	231	3.5	8.7	6.9	6.1	25.1
1930–1944	799	0.0	1.6	0.1	0.9	2.6
Itú						
1842–1850	256	2.3	7.8	2.7	4.7	17.6
1936–1947	1293	0.1	0.7	0.8	0.1	1.6
São Roque						
1837–1850	168	1.2	10.7	0.0	4.2	16.1
1944–1947	230	0.0	1.3	0.4	0.9	2.6
Itaquaquecetuba						
1835–1854	128	0.0	5.5	0.8	5.5	11.7
Guarulhos						
1831–1851	207	1.5	8.2	2.9	5.3	17.9
Jundiai						
1842–1851	205	0.0	4.9	1.5	6.8	13.2
Cabreuva						
1832–1856	157	2.5	10.8	2.5	6.4	22.3
São Bernardo						
1836–1850	148	0.0	9.5	3.4	12.8	25.7
Ibiuna						
1836–1853	196	3.6	15.8	5.6	6.1	31.1
Santana do Parnaiba						
1831–1850	162	3.1	8.6	2.5	8.6	22.8
Araçariguama						
1830–1852	125	4.0	15.2	7.2	6.4	32.8

This relative isolation of the Freguesia do Ó has resulted in a high proportion of consanguineous marriages. Indeed, a century ago as many as 11.4 per cent of the marriages there were concluded between first cousins, while, at the same time, only 5 per cent of the marriages at Santa Efigenia were between first cousins. With the rapid expansion of the city, the frequencies of consanguineous

TABLE 4. FREQUENCY, IN PER CENT, OF MARRIAGES BETWEEN RELATIVES IN THE PARISH OF APARECIDA DO NORTE. THE DATA ARE GIVEN SEPARATELY FOR THE INHABITANTS OF THE PARISH AND FOR THE NON-RESIDENTS

TIME	N	UNCLE-NIECE & AUNT-NEPHEW	FIRST COUSINS	SECOND COUSINS	THIRD COUSINS	TOTAL
Inhabitants						
1904–1919	367	0.0	0.8	0.3	0.3	1.4
1919–1929	366	0.0	1.1	0.3	0.8	2.2
1929–1940	359	0.0	1.1	0.3	0.3	1.7
1940–1949	527	0.0	0.9	0.4	0.2	1.5
Non-res.						
1910–1915	794	0.4	7.3	1.8	2.2	11.7
1915–1919	797	0.4	7.2	2.5	3.0	13.1
1919–1922	1199	0.2	6.0	1.6	1.5	9.3
1922–1925	1196	0.2	4.2	1.2	1.3	6.9
1925–1927	1200	0.1	4.2	1.0	1.5	6.8
1927–1930	1200	0.0	4.3	0.9	1.7	6.9
1930–1936	1569	0.1	4.8	1.3	1.2	7.4
1936–1940	2000	0.0	4.7	1.2	1.9	7.8
1940–1945	2400	0.0	2.2	0.9	1.4	4.5
1945–1949	3745	0.1	1.9	0.5	1.1	3.6

TABLE 5. FREQUENCY, IN PER CENT, OF MARRIAGES BETWEEN RELATIVES IN THE STATE OF MINAS GERAIS

TIME	N	UNCLE-NIECE & AUNT-NEPHEW	FIRST COUSINS	SECOND COUSINS	THIRD COUSINS	TOTAL
Parish of Boa Esperança						
1932–1934	231	0.0	6.5	4.7	0.9	12.1
1935–1937	211	0.0	7.1	0.5	3.3	10.9
1939–1941	265	0.0	6.8	1.1	3.0	10.9
1944–1946	282	0.0	4.6	1.1	2.8	8.5
1948–1949	211	0.0	4.7	0.5	1.0	6.2
Parish of Varginha						
1929–1933	559	0.2	1.6	0.9	1.4	4.1
1940–1944	625	0.0	2.1	1.7	1.6	5.4
1945–1947	603	0.0	1.5	1.5	1.3	4.3
1948–1951	640	0.0	2.9	1.3	0.6	4.8
Diocese of Campanha (about 50 parishes)						
1939	2,913	0.1	6.4	2.2	2.3	10.9
1940	2,858	0.1	5.7	1.9	2.7	10.4
1941	3,005	0.1	5.0	1.2	2.4	8.7
1942	2,791	0.1	5.4	2.8	2.6	10.9
1943	2,754	0.1	5.8	2.5	2.9	11.3
1944	3,142	0.0	6.3	2.2	3.7	12.2
1945	3,162	0.0	5.7	2.3	2.9	10.9
1946	3,238	0.1	5.9	2.4	3.0	11.4
1947	3,737	0.0	3.5	1.9	2.5	7.9
1948	4,572	0.0	3.4	1.5	2.6	7.5
1949	3,843	0.0	5.2	1.7	2.3	9.2
1950*	3,440	0.1	5.8	1.5	2.7	10.1

* Incomplete data

marriages at Freguesia do Ó declined rapidly and are at present not very different from those at Santa Efigenia, namely, around 0.5 per cent.

Another contrast is between the small towns in the State of São Paulo, and those in the State of Minas Gerais. The former are all relatively close to the state capital, which has at present more than two million inhabitants. The latter are remote from the state capital, Belo Horizonte, with only some 360,000 inhabitants, and lie in the valley of the upper Parnaiba River (Diocese of Uberaba) and in the southern part of the state (Diocese of Campanha).

TABLE 6. FREQUENCY IN PER CENT OF MARRIAGES BETWEEN RELATIVES IN THE DIFFERENT PARISHES WITHIN THE STATE OF MINAS GERAIS DURING THE PERIOD 1948–1949 (DIOCESE OF UBERABA).

PARISH	N	FIRST COUSINS	SECOND COUSINS	TOTAL
Campina Verde	322	10.3	4.4	14.7
Romaria	107	8.4	0.9	9.3
Carmo do Paranaiba	234	7.7	1.3	9.0
Perdizes	151	6.0	1.3	7.3
Ibiá	96	5.2	2.1	7.3
Presidente Olegario	297	5.1	4.7	9.8
Sacramento	201	5.0	1.5	6.5
Araxá	297	3.7	—	3.7
Patos	506	3.5	1.2	4.7
Estrela do Sul	199	3.5	3.0	6.5
Patrocinio	282	2.8	0.0	2.8
Uberaba	635	2.5	1.1	3.6
Sta. Ana dos Patos	88	2.3	0.0	2.3
Conquista	106	1.9	0.0	1.9
Frutal	181	1.7	0.0	1.7
Coromandel	264	1.5	1.1	2.6
Tupaciguara	240	1.3	0.8	2.1
Prata	90	1.1	5.6	6.7
Monte Carmelo	185	1.1	0.5	1.6
Araguari	563	1.1	—	1.1
Uberlândia	602	0.7	0.7	1.4
	5,646	3.3	1.5	

Within Minas Gerais, the Diocese of Campanha is one of the most prosperous parts of the state, with fairly developed business activities. The region of the upper Parnaiba (the Diocese of Uberaba) is, on the other hand, a stock-raising country. These regions show very high frequencies of consanguineous marriages. The lowest frequencies are found in towns of the State of São Paulo and in São Paulo City.

A very interesting situation is disclosed by the data for Aparecida do Norte. The frequencies of consanguineous marriages between the residents of this parish have been, during the last 45 years, much lower than those among the natives of other parishes who come there to have their marriages consecrated. During the period from 1904 to 1949 the first cousin marriages among resi-

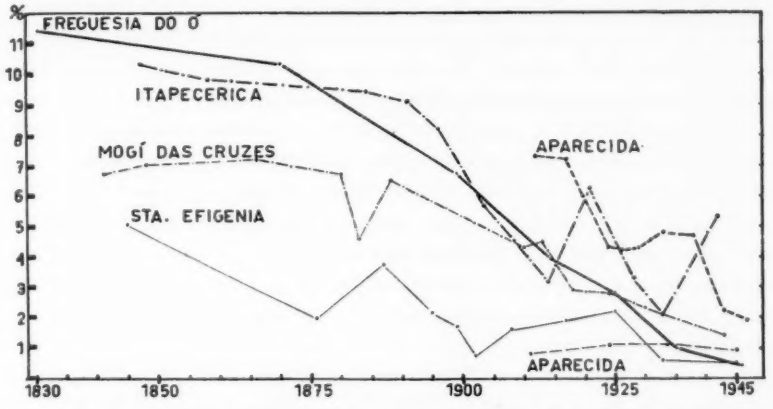

FIG. 1. Frequencies of marriages between first cousins in certain Brazilian populations at different times. The upper curve for the town of Aparecida do Norte represents marriages between visitors and the lower curve those between residents in the parish.

TABLE 7. FREQUENCIES, IN PER CENT, OF MARRIAGES ACCORDING TO THE PARISH OF BIRTH OF THE BRIDE AND GROOM

PARISH	PERIOD	WH	wH	Wh	wh	*wh*	N	PARISHES		INDEX
								same	dif.	
Sta. Efigênia (São Paulo city)	1924	5.4	7.7	14.6	64.6	7.7	130	13.1	86.9	6.63
	1941–'42	0.7	4.5	11.3	78.2	5.3	133	6.0	94.0	15.67
Fr. do Ó (São Paulo city)	1926–'28	10.0	10.8	23.3	51.7	4.2	120	14.2	85.8	6.04
	1944–'45	5.6	7.2	10.4	70.4	6.4	125	12.0	88.0	7.33
Mogi das Cruzes	1912–'13	49.5	7.6	20.3	16.7	5.9	222	55.4	44.6	0.81
	1923–'25	45.2	10.2	20.7	19.8	4.1	217	49.3	50.7	1.03
	1933–'34	47.9	9.2	21.7	20.7	0.5	217	48.4	51.6	1.07
	1940–'41	40.4	13.9	18.4	26.0	1.3	223	41.7	58.3	1.40
	1946	27.3	14.1	23.2	31.8	3.6	220	30.9	69.1	2.24
Itapecerica	1918–'20	92.8	2.7	4.5	0.0	0.0	112	92.8	7.2	0.08
	1929–'31	80.3	2.0	12.9	4.8	0.0	147	80.3	19.7	0.25
	1942–'44	75.9	5.7	14.9	3.5	0.0	141	75.9	24.1	0.32
Parnaiba	1920–'23	43.8	5.5	24.2	23.4	3.1	128	46.9	53.1	1.13
	1945–'47	19.6	14.5	21.0	43.5	1.4	138	21.0	79.0	3.76
Aparecida do Norte (parishioners)	1919–'23	16.1	16.1	23.1	38.4	6.3	143	22.4	77.6	3.46
	1931–'36	13.2	11.8	34.0	30.6	10.4	144	23.6	76.4	3.24
	1943–'45	7.5	19.7	24.5	39.5	8.8	147	16.3	83.7	5.13
Boa Esperança	1933–'35	72.4	7.8	11.4	6.6	1.8	167	74.2	25.8	0.35
	1936–'38	72.9	8.4	14.5	2.3	1.9	214	74.8	25.2	0.34
	1947–'48	39.3	16.8	27.6	12.6	3.7	214	43.0	57.0	1.33

dents oscillated around 1 per cent, while among the outsiders they amounted to more than 7 per cent between 1910 and 1919 and fell only in recent years to 1.9 per cent. This suggests that the isolate of Aparecida do Norte has been much greater during this period than could have been supposed on the basis of the low population of the parish. In fact, the cousin marriages among the residents of Aparecida do Norte were less frequent than among the inhabitants of the two parishes in the city of São Paulo. These facts can be understood easily by taking into account the religious importance of the locality. For several decades Aparecida do Norte has been visited daily by many pilgrims. The magnitude of these movements can be estimated approximately by comparing the annual figures for the marriages between local residents and between visitors. Between 1940 and 1949 approximately 680 marriages per year were registered between outsiders, while during the same period the numbers of marriages in which at least one party was a local inhabitant did not exceed 60 per annum. A similar disproportion obtained, also, during earlier periods. For example, between 1919 and 1927, 420 marriages were registered annually between outsiders and only 34 marriages between residents. Examination of the figures for Aparecida do Norte in Table 7 discloses, then, the explanation of the relative rarity of consanguineous marriages in that parish. During the period 1919–1923, the marriages in which both parties were born in the parish of Aparecida constituted only 16 per cent of the marriages in which at least one of the parties resided in Aparecida. More recently this percentage has fallen to 7.5 per cent. These percentages are extremely low compared to what is observed in other interior towns, although some of the latter, such as Mogi das Cruzes, have much greater populations.

DISCUSSION

To explain the high frequencies of consanguineous marriages in Japan, Neel, Kodami, Brewer and Anderson (1950) point out that, in that country, the marriages are often arranged by the parents of the prospective bride and groom. The parents and relatives tend to make matches among members of family or clan. In the nineteenth century, a similar situation also obtained in Brazil. At present, we like to believe, this factor is of little importance in Brazilian populations which we have analyzed. The persistence of relatively high frequencies of consanguineous marriages in Brazil must, then, be interpreted as a result of the rather low population density and of poor means of communication, at least in comparison to European countries. The small towns, villages, and especially the ranches, still remain to some extent isolated from each other. In addition to the isolation, the smallness of human isolates in Brazil is maintained by social and racial prejudices.

Still another factor which tends to increase the frequencies of consanguineous marriages is that Brazilian families are, on the average, much larger than

European ones. In the great metropolitan centers of Rio de Janeiro and São Paulo the mean number of marrying children per family is close to 3. In small towns of the interior and in rural districts this number is greater, probably between 4 and 5. To be sure, the birth control practices which have started to spread in recent times tend to lower these figures.

An attempt may be made to compute the mean frequency of first cousin marriages in Brazil. On the basis of the data discussed above, the frequency may reasonably be assumed to lie in the vicinity of 5 per cent. On the other hand, the average number of marrying children per family is close to 4. Dahlberg (1929, 1949) has proposed the following formula to calculate the mean size of an isolate in a population:

$$n = 2b(b - 1)/C,$$

where b is the average number of marrying children per family, and C the frequency of cousin marriages. Using the above formula, the mean size of Brazilian isolates turns out to be about 500. This is a much lower figure than that derived by Dahlberg for European isolates (1600).

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SUMMARY

Data on the frequencies of consanguineous marriages in certain populations in Brazil are summarized in tables 1–7 and in figure 1. These frequencies are greater in rural than in urban populations. A clear trend towards lower frequencies of consanguinity is observed in most parishes with time. The human isolates are smaller in Brazil than in European countries, according to the data of Dahlberg.

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Absence of Linkage Between the Genes Responsible for the Sickling Phenomenon, the MN Blood Types, and the S-agglutinogen[1]

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SNYDER, RUSSEL, AND GRAHAM (1947) and Snyder, Clarke, and Moore (1949) have reported autosomal linkage in the American Negro between the genes responsible for the sickling phenomenon and the MN blood types. Sanger and Race (1947), Sanger, Race, Walsh and Montgomery (1948) and Race, Sanger, Lawler, and Bertinshaw (1949) have established the existence of a human ag-

TABLE 1. METHOD OF DESIGNATING THE GENOTYPES:

	Normal *sksk*	Sickle cell trait *Sksk*	Sickle cell disease *SkSk*
MM	a_{11}	a_{12}	a_{13}
MN	a_{21}	a_{22}	a_{23}
NN	a_{31}	a_{32}	a_{33}

a. Where *M* and *N* represent the genes responsible for the respective blood antigens, and *sk* and *Sk* represent the genes responsible for normal red blood cells and those exhibiting the sickling phenomenon.

	S-negative *ss*	S-positive *Ss* or *SS*
Normal *sksk*	b_{11}	b_{12}
Trait *Sksk*	b_{21}	b_{22}
Disease *SkSk*	b_{31}	b_{32}

b. Where *S* represents the gene responsible for the S-reaction and *s* its recessive allele, and *Sk* and *sk* have the same significance as above.

glutinogen termed S, which is non-randomly associated with the MN blood types, the relationship permitting of two explanations: (1) there are four alleles, *MS*, *M*, *NS*, and *N*, or (2) there is a pair of alleles, *S* and *s*, closely linked to the genes responsible for the MN blood types, no recombination having

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TABLE 2. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE MN BLOOD TYPES, IN FAMILIES WHERE BOTH PARENTS WERE STUDIED

MATING NUMBER	FINNEY MATING TYPE	a_{11}	a_{12}	a_{13}	a_{21}	a_{22}	a_{23}	a_{31}	a_{32}	a_{33}	a	b	c	d	s	SCORE	VARIANCE
2	20							1	1		1		1		2	−1	1
6	21	1	1				1					1	1		2	1	1
19	21				1				2			2			2	1	1
22	21				1	1	1	2			1	1	2		4	0	6
39	21				1	2				1	1			1	2	1	1
48	21				1	1	1				1	1			2	−1	1
53	21						2					2			2	1	1
57	21					2	2			1		2		1	3	−1	3
64	21				1	2	1		2		1	1			2	−1	1
79	21		3		1			1	1		3	1		1	5	2	10
81	21	1		1		1	1					1	1	1	3	−1	3
90	21				2	1					2				2	1	1
91	21				1	2	2				1	2			3	−1	3
93	21						2	1	1	1		2	1	1	4	0	6
98	20				1	1		1	1		1	1	1	1	4	−2	6
99	20				3	1		3				1	3	3	7	−3	21
110	21						2					2			2	1	1
111	21	1	2		3	3		1	3		2	3	1	1	7	−3	21
113	22			1		1				1			1	1	2	−2	4
118	20	3	1		1						1		3	1	5	−2	10
20-S	21	1	1	1									1	1	2	−1	1
26-S	20				1				1		1			1	2	1	1
31-S	20					1			2		2	1			3	−1	3
32-S	20		1			1					1	1			2	−1	1
Total															74	−12	108

TABLE 3. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE MN BLOOD TYPES, IN FAMILIES WHERE ONLY ONE PARENT WAS TESTED AND WAS HETEROZYGOUS FOR BOTH FACTORS

MATING NUMBER	a_{11}	a_{12}	a_{13}	a_{21}	a_{22}	a_{23}	a_{31}	a_{32}	a_{33}	A_1	A_2	A_3	P_1	P_2	P_3	A	k
2-S							1	1			−1	−1		.3333	.6667	−1.000	1.000
8-S	1	2	1	2						−1	−2		.8889	.1111		−1.111	13.111
11-S	1	1		1	1					−2	−1		.6667	.3333		−1.667	3.222
22-S				1	2	2				−2	0	−2	.2500	.5000	.2500	−1.000	2.500
23-S	1			1			1	1			−1			1		−1.000	3.000
28-S		2								1	1		.6667	.3333		1.000	1.000
100			1	1	1					1	0		.5000	.5000		.500	.750
29	1			1	1		2	1			−2			1		−2.000	6.000
30					1	1	1				0	−1		.5000	.5000	−.500	.750
31				3	3		1				−3	0		.5000	.5000	−1.500	5.250
36					2					1	0	1	.2500	.5000	.2500	.500	.250
44				1			1	1	1		−2	−1		.2000	.8000	−1.200	4.920
46	1		1		3					6	−2		.6667	.3333		3.000	5.000
Total																−5.978	46.753

been observed among 82 relevant children. If the latter interpretation is correct, then from the studies of these two groups of investigators emerges the possibility of an autosomal linkage group in man composed of three genes with clear cut effects.

Recent investigations in this laboratory have established the fact that the sickling phenomenon of the erythrocytes of the American Negro is due to a gene (*Sk*) which in heterozygotes produces the apparently harmless sickle cell trait and in homozygotes the more serious sickle cell disease (Neel, 1949, 1951). The exact genetic relationship between the sickle cell trait and sickle cell disease was not known to Snyder et al at the time of their studies, and both trait and disease were considered to be variable manifestations of the same dominant gene.

TABLE 4. TEST OF LINKAGE BETWEEN THE GENES RESPONSIBLE FOR THE SICKLING PHENOMENON AND THE S-REACTION, IN FAMILIES WHERE BOTH PARENTS WERE TESTED

MATING NUMBER	FINNEY MATING TYPE	b_{11}	b_{12}	b_{21}	b_{22}	b_{31}	b_{32}	a	b	c	d	s	SCORE	VARIANCE
6	4		1		1	1		1			1	2	1	1
22	4	2	1		1		1	1	1	2		4	0	6
39	4		1		2	1		1			1	2	1	1
48	4	1		1		1				1	1	2	−1	1
57	4			2		3					3	3	3	3
79	3	2		1	3				3	2	1	6	5	15
40	4					1	1		1		1	2	−1	1
55	4	1	1	4			2	1	2	1		4	0	6
59	3	2	2	1	2			2	2	2	1	7	−3	21
65	4		1	2			2	1	2			3	−1	3
Total												35	4	58

In connection with our studies on the genetics of the sickling phenomenon in the American Negro, we have had occasion to accumulate additional data bearing on the question of linkage between the *Sk* and *MN* and *S* genes. Through the kindness of Dr. R. R. Race we have had available for our use a limited quantity of anti-S serum. That portion of our data bearing on the relation between the M-N and S reactions in American Negros has already been presented (Neel and Hanig, 1951). In corroboration of the findings of others, the two alternative possible relationships mentioned above between *M-N* and *S* were confirmed, no recombination being observed in 18 relevant children. The present paper will analyze the linkage relationships of the *Sk* gene to the *M-N* and *S* genes. In the analysis, the M-N and S reactions will be treated as if determined by separate albeit closely linked genes.

Material. The findings in those of the families in our series which yield in-

formation relevant to the question of linkage are summarized in tables 2, 3, and 4. The children in these families have been scored as to the information they yield concerning linkage according to the method proposed by Finney (1940, 1941). Table 1 presents the code designations used to describe the children. From these code designations plus a knowledge of the Finney mating types, the exact composition of any family can be reconstituted.

Discussion and Conclusions. The present data provide no evidence for a linkage between the *Sk* gene and those responsible for either the M-N or S reactions, the *u*-scores for *Sk* and *MN* being negative (tables 2 and 3), and for *Sk* and *S* positive but well below the level of significance (table 4).

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Applicability of the Twin Study Method in the Analysis of Variations in Mate Selection and Marital Adjustment[1]

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IT has long been apparent that the phenomena of marriage and parenthood have too many and too important ramifications to be dealt with by a single discipline or by a synthetic conglomeration of the human sciences. In the last analysis, the organization of stable societies rests largely on the acceptance of marriage as a basic institution. The preservation of this institution is so vital for the maintenance of the biological, cultural and moral values of human heritage that it must be guarded from the repercussions of frequent changes in social customs, ethnic stratifications and reproductive capacities. Evidently, no one class of super-specialists can consider itself sufficiently competent and self-reliant to claim a monopoly on all the scientific and philanthropic resources required for an adequate understanding or the professional management of the phenomenological problems arising from family relations.

In terms of personal interrelationships, the procurement of interdisciplinary guidance in relation to marriage and reproduction is equally important. The need of this service is obvious if one bears in mind that the degree of individual adjustment and mental health attainable on an adult level appears to be more dependent on "the wise choice of a life partner" than on any other single factor (Baber, 1937). It is rather unfortunate, therefore, that large segments of scientific workers, professional organizations and public health agencies are still inclined to cling to an attitude of timid inactivity, ideological compartmentalization or cynical indifference when confronted with some of the complexities of family relationships and population policies. If interdisciplinary approaches to the problems of mate selection, marital adjustment and parenthood are a necessity in modern societies, it is even more imperative that they should be plainly decodified and resolutely integrated.

Methodologically, all investigative procedures used are to proceed on the general premise that marriage and fertility reflect practically the entire range of potential human imperfections in biological adaptation, emotional adjustment, and social security. It is utterly inappropriate, of course, to blame the

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institution of marriage for universal inadequacies of human existence, merely because certain matings are apt to intensify pre-existing shortcomings, conflicts and frustrations (Fishbein & Burgess, 1947). Therefore, the current tendency to advocate "complete abolition of the authority of the family" for the purpose of eliminating at the roots all the social and mental ills of human culture (Neill, 1949) is ill-advised to the same extent as has been the ancient practice of encouraging marriage as an expedient "cure-all" for every conceivable form of maladjustment. Such pseudo-heroic solutions stem from the uncontrolled projection of sentimental allergies or personal disappointments and merely confirm the fact that scholarly pursuits and professional philanthropies may serve as powerful tools of sublimating compulsions.

In a more realistic appraisal of the dynamics of marital adjustment and reproduction, it is advisable to start with the observation that the broad potentialities of these phenomena depend on a great number of selective (restrictive) factors which tend to determine the choice of a mate. Irrespective of whether the prevailing forms of *mate selection* are essentially assortative or largely preferential in their effect, they are known to be subject to conscious as well as to unconscious motivations and, therefore, are certain to have an important bearing on the outcome of marital ventures (Anshen, 1949). As a rule, preferential criteria of mate selection are traceable to an effort to ensure success of a marriage by means of parental approval and through a comparison of the qualities of a prospective mate with those of the given parental types (Hamilton, 1929). Marital life is believed to be easier if parents approve, although "neither the law nor social expectation demands that they should" (Mead, 1949).

In modern societies, the multiple relationships between factors of mate selection and the prospects of marital adjustment have become so intricate that satisfactory insight into this important interplay cannot possibly be gained either by generalized inferences from some casuistic and experiential observations or by any statistical analysis of general census figures related to the differential marriage and fertility rates of entire population groups. When human phenomena are corollaries of individual patterns of personality development and basically depend on a complex interaction of biological and social elements susceptible to profound and continuous differences, general conclusions should not be drawn from a comparison of persons or population samples distinguished by many inconsistencies in genetic, cultural and psychological background factors. The disentangling of such a multiplicity of determining influences requires the employment of specialized investigative procedures, which assure us of a relatively constant environment while the genotype varies and, conversely, of a relatively constant genotype while the environment varies (Kallmann, 1951; Kallmann & Feingold, 1951; Muller, 1949).

One of the most promising procedures available for this task of disentanglement is the *twin study method*, especially if a flexible and easily adjustable modification is used, called *the twin family method*. The main advantage of this modified procedure is that it provides the largest possible scale of genetically dissimilar sibship groups, whose environmental conditions can be directly compared and evaluated (Kallmann & Sander, 1949).

Since the principal objective of our research organization during the past fifteen years has been that of procuring longitudinal records on the life histories of adult twin pairs in the State of New York, we are able to offer a few technical clues to the procedure by which twin studies may be used for a comparative analysis of data on marriage and reproduction. In relation to the range of the marital problems investigated it may be borne in mind, however, that a collection of data on family relations under normal and abnormal circumstances has not been the primary goal of our surveys. Therefore, the limited purpose of this report may be seen in an attempt to demonstrate some promising avenues of approach to marriage problems rather than to inquire into their entire scope.

With respect to *ordinary variations* in marital twin data observable in the absence of specific psychopathological complications, one of the obvious prerequisites consisted of nearly completed and comparatively unselected life histories of normal twin groups of either zygocity. Such a sample was available in a series of approximately 1200 senescent twin index cases (over age 60), who had never been admitted to a mental hospital or any other institution, including a home for the aged. In the interest of direct statistical comparability, another requirement of the sample was seen in its limitation to index pairs, who were of the same sex and resided in the State of New York. The marital and reproductive data observed in this series of 240 normal, senescent twin index cases (120 pairs) have been compared in table 1 with the corresponding data for those of their sibs (290) who had also reached an age of 60 years.

The comparison reveals no significant differences between twins and single-born members of the same family units with respect to *celibacy*, *childlessness* in marriage, and the proportion of *fertile marriages*. About 70 per cent of the twins and their sibs were married and had at least one child. The most important implication of this finding is that the marriage data of twin family units may be regarded as representative of the *total population*. The general validity of this conclusion is supported by the fact that the celibacy rate of 11.7 per cent for the sibs of aging twins corresponds closely with the 1940 Census rate of 11.6 per cent for the general population of the State of New York over age 60. It may also be noted that the small differences between our total groups of twins and sibs are not statistically significant.

It is in accordance with statistical expectation that the main discrepancies in the celibacy rate in relation to the various groups of twin index cases (rather

than of twin index pairs) are observed between the two sexes and not between the two types of twins. The celibacy rates of the total groups of monozygotic and dizygotic twins vary only from 12.5 to 14.2 per cent, while the difference between male and female twins is from 9.2 to 17.5 per cent.

TABLE 1. CLASSIFICATION AS TO MARITAL STATUS OF A SAMPLE OF NORMAL TWIN INDEX CASES (240), TWIN INDEX PAIRS (120) AND THEIR SIBS (290)

a) *Twin Index Cases*

		Single	Married Childless	Married with Children	
♂	MZ	4	14	42	60
	DZ	7	11	42	60
		11	*25*	*84*	*120*
♀	MZ	11	9	40	60
	DZ	10	12	38	60
		21	*21*	*78*	*120*
Both sexes	MZ	15	23	82	120
	DZ	17	23	80	120
		32	*46*	*162*	*240*
Both zygocity classes	♂	11	25	84	120
	♀	21	21	78	120
		32	*46*	*162*	*240*

b) *Twin Index Pairs*

		Both Single	One Married	Both Married	
♂♂ Pairs	MZ	0	4	26	30
	DZ	2	3	25	30
		2	*7*	*51*	*60*
♀♀ Pairs	MZ	4	3	23	30
	DZ	2	6	22	30
		6	*9*	*45*	*60*
Both sexes	MZ	4	7	49	60
	DZ	4	9	47	60
		8	*16*	*96*	*120*
Both zygocity classes	♂♂	2	7	51	60
	♀♀	6	9	45	60
		8	*16*	*96*	*120*

c) *Sibs Over Age 60*

	Single	Married Childless	Married with Children	
♂	13	27	104	144
♀	21	18	107	146
	34	*45*	*211*	*290*

d) *Celibacy in Per Cent*

	Twin Index Cases	Twin Index Pairs	Sibs
♂	9.2	3.3	9.0
♀	17.5	10.0	14.4
	13.3	*6.7*	*11.7*

The corresponding data relative to the marital status of index pairs are presented in the second part of table 1. In each group, the percentage of pairs with one married member may be taken as a measure of intra-pair difference in marital status. If this percentage is low, the intra-pair similarity is high, and vice versa. Hence, monozygotic pairs appear to be more similar than dizygotic pairs, and male pairs may be more similar than female pairs. In other words, it seems to happen more frequently in female than in male pairs that one twin is single and the other married, and a similar difference is ob-

served between the total groups of dizygotic and monozygotic pairs (15.0–11.7 per cent). However, the available samples are numerically limited and will need enlargement before a more definite statement can be made about the significance of these data on marital status.

Another point of interest may be seen in the fact that the present sample includes no monozygotic pair of twin brothers, both of whom were unmarried. A possible reason for this observation appears to be that unmarried males, if they are alike in their personalities and tend to form a social and residential unit, are less likely than pairs of unmarried females to remain outside of institutions during the senescent period. In any case, if one includes all institutionalized twins over 60 years of age as was done in a previous analysis (Kallmann and Sander, 1949), the proportion of monozygotic male twin pairs concordant as to celibacy is found to be 11.3 per cent. It is possible, therefore, that some of this difference in the proportion of celibate pairs, as observed in relation to both sex and zygocity, tends to reflect the part played by heredity in determining those aspects of personality development which affect the individual attitude toward marriage.

There is no indication that closeness between sibs is likely to reduce their prospects of marriage. The possibility of such an explanation for some apparent differences in the comparative celibacy rates of the present sample is precluded by the observation that in approximately 80 per cent of the total group of twin pairs included in the analysis, both partners have been married.

While most of the differences in the percentage distribution of the data on marital status as computed in table 1 fail to reach the level of statistical significance and, therefore, are useful mainly for general methodologic rather than specific inferential purposes, there is one interesting observation which fulfils the requirements of the chi-square test, with one degree of freedom, and has a definite bearing on the dynamics of mate selection. The procedure to be applied in this analysis was suggested by Dr. C. W. Cotterman and was used in a recent study of ankylosing spondylitis (Hersh and others, 1950).

If the total group of 120 twin index pairs (60 ♂♂, 60 ♀♀) is classified according to marital status, one obtains the ratio 8:16:96 for both-single: one-married: both-married pairs (table 1b). In subjecting this ratio to the chi-square test, one is able to determine whether or not there are more pairs concordant as to marital status than one would expect on the assumption of independent probabilities for marriage.

The appropriate formula is

$$X^2 = \frac{120(16^2 - 4 \cdot 8 \cdot 96)^2}{(2 \cdot 8 + 16)^2 (16 + 2 \cdot 96)^2} = 21.5, \quad \text{and} \quad P < 0.001.$$

One may say, therefore, that the proportions of twin pairs concordant as to marital status (both married or both single) are too frequent to allow one

to assume that the probability of a twin's marrying is independent of that of his or her twin partner.

The comparative data on *reproductiveness* in married twin pairs of the same sex are summarized in table 2. Evidently, these data do not confirm the old superstition that one of identical twin brothers is doomed to be sterile. In

TABLE 2. MARITAL FERTILITY OF NORMAL, SAME-SEXED TWIN INDEX PAIRS (96) OVER AGE 60

a) *Reproductiveness*

		Both Childless	One Childless	Both with Children	
♂♂	MZ	1	10	15	*26*
	DZ	2	7	16	*25*
		3	*17*	*31*	*51*
♀♀	MZ	2	5	16	*23*
	DZ	—	8	14	*22*
		2	*13*	*30*	*45*
Both sexes	MZ	3	15	31	*49*
	DZ	2	15	30	*47*
		5	*30*	*61*	*96*
Both zygocity classes	♂	3	17	31	*51*
	♀	2	13	30	*45*
		5	*30*	*61*	*96*

b) *Average Number of Children*

		One Childless	Both with Children
♂♂	MZ	3.1	3.1
	DZ	3.0	3.2
♀♀	MZ	1.6	3.5
	DZ	2.3	2.9
Both sexes	MZ	2.6	3.3
	DZ	2.6	3.1
Both zygocity classes	♂	3.1	3.1
	♀	2.0	3.3

c) *Average Intra-Pair Difference in Number of Children*

		All Married Pairs (96)	All Fertile Pairs (61)
♂♂	MZ	2.2	1.7
	DZ	2.4	2.5
Both sexes	MZ	1.9	1.7
	DZ	2.1	2.0

		All Married Pairs (96)	All Fertile Pairs (61)
♀♀	MZ	1.5	1.6
	DZ	1.7	1.4
Both zygocity classes	♂	2.3	2.1
	♀	1.6	1.6

almost 60 per cent of married monozygotic twin brothers, the marriages of both twins are found to have been fertile.

With respect to the proportion of twin pairs wherein one partner had children while the other had none, the present analysis reveals no evidence of a significant difference between the total groups of monozygotic and dizygotic pairs (30.6 and 31.9 per cent, respectively). However, it appears that child-

lessness of one twin is more frequent in monozygotic than in dizygotic twin brothers (38.5 and 28.0 per cent), and less frequent in monozygotic than in dizygotic twin sisters (21.7 and 36.4 per cent). The given differences do not reach the level of statistical significance and, therefore, require re-examination in larger samples. The need of such additional comparative investigations is especially obvious, if one considers that there seem to be equally interesting intra-pair differences in the number of children produced by married twin pairs concordant as to reproductiveness.

While the intra-pair differences in the fertility of monozygotic and dizygotic twin pairs (table 2c) are 1.7 and 3.6 children, respectively, in the male pairs and 1.6 and 1.4 children, respectively, in the female pairs, the average intra-pair differences in the fertility of the two zygocity groups (irrespective of sex) are 1.7 and 2.0 children. Thus, married monozygotic twin partners seem to differ less in the number of children they produce than do married dizygotic twin partners, particularly if the twins are of male sex.

If confirmed, these findings would disagree with the popular notion that the female partner is the chief determining factor in the regulation of family size. However, there are certain indications that the significance of the female partner exceeds that of the male partner with respect to the difference between childlessness and fertility of a marriage.

From a practical standpoint, particular importance is attached to an attempt to investigate the potential usefulness of the twin study method in relation to those variables in *mate selection* and *marital adjustment* which are usually assumed to influence the outcome of a marriage more immediately than is true for variations in reproduction. A qualitative analysis of two comparable groups of married normal twin index pairs (40 monozygotic and 40 dizygotic index pairs, equally divided according to sex) has, therefore, been undertaken with reference to the following presumably correlative features: (*a*) Age of the twins at the time of their first marriage, (*b*) ages of their respective mates, (*c*) duration of marriage, (*d*) religion, (*e*) nationality, (*f*) socio-economic status, and (*g*) degree of marital adjustment (Mowrer & Mowrer, 1947).

The intra-pair differences between monozygotic and dizygotic groups are compared in figure 1 with regard to the *marriage ages* of twin partners and the respective ages of their mates. The comparison reveals a definite difference between the two groups in that 80 per cent of monozygotic twin partners and only 55 per cent of dizygotic twin partners are reported to have married within five years of one another. Such a difference would not seem to be entirely without effect upon the outcome of the given marriages. However, if this age difference is related to the degree of marital adjustment, it appears to have been without correlative significance.

The same is true for age differences between the *first mates* of twin partners, if only because there is little difference between monozygotic and dizygotic

twin pairs with respect to the tendency to choose mates of similar age. It is shown in the second part of figure 1 that the ages of the mates of twins differ by less than five and one-half years in 60 per cent of the one-egg pairs and in 55 per cent of the two-egg pairs. In line with this finding, it has been established by Burgess and Cottrell (1939) that age differences between spouses cannot be expected to be a major determining factor as to marital adjustment, at least for the first six years of marriage and if the marriages are contracted within the period of maturity. There is no evidence in the present material, which disagrees with this general rule.

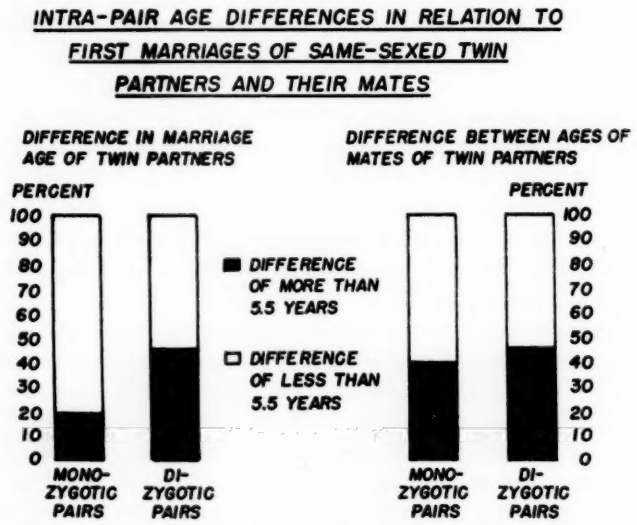

FIG. 1. Intra-pair age differences in relation to first marriages of same-sexed twin partners and their mates.

However, an interesting difference in mate selection is found between the two groups of twins, if one compares the socio-economic background factors of their mates. The comparative results are shown in figure 2. They have been obtained in such a way that differences between the mates of twin partners are rated on a seven-point scale (0–6). A difference of three steps has been called "marked," and a difference of one or two steps appears as "moderate." The classification called "no dissimilarity" implies that the mates of both twin partners came from practically the same socio-economic category. No difference in excess of three steps has been observed in our sample.

It is revealed by a careful application of this scheme that 40 per cent of monozygotic twin partners and 30 per cent of dizygotic twin partners selected mates who did not differ in their socio-economic status. However, there is a

marked difference between the backgrounds of the mates in 10 per cent of the dizygotic pairs, while such an extensive difference does not occur in the monozygotic group. There is reason to believe, therefore, that the generally observed tendency toward marriage within a certain socio-economic group (Centers, 1949) is especially pronounced, if prospective marriage partners are alike in their type of personality.

It is essential to note, however, that according to the observed variations in *marital adjustment*, a greater similarity in the backgrounds of the mates of one-egg twin partners does not seem to express itself in a more satisfactory degree of marital adjustment than is found in the dizygotic group, at least within the limits of variability discernible in the present sample with respect to dissimilarity in the racial, cultural and social background factors of the

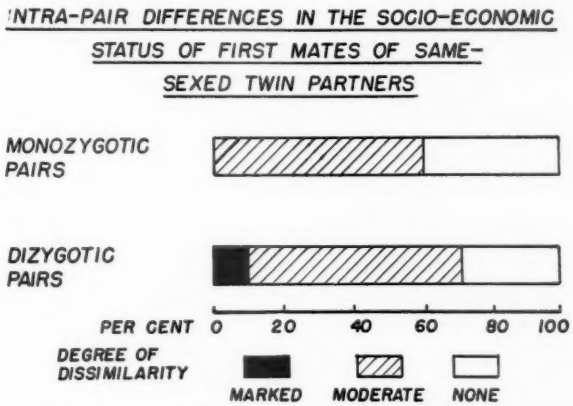

FIG. 2. Intra-pair differences in the socio-economic status of first mates of same-sexed twin partners.

spouses. As stated before, the present material includes no variations between mates of twin partners in either group of twins, which exceed a difference of three steps in any of these factors. Significant differences in such general background factors do not occur between the two members of one-egg pairs, and the differences observed in the group of two-egg pairs are usually limited to moderate dissimilarities in educational or occupational status.

In spite of pronounced similarities in a great number of factors qualifying the environments of monozygotic twin partners and their mates, there is no significant difference between the two groups of twins in relation to the proportion of pairs discordant as to poor marital adjustment. If the quality of adjustment is classified as poor, medium or good, about 20 per cent of the pairs in either group reveal differences in the degree of marital adjustment ranging from poor to medium or from poor to good. It may be said, therefore,

that complete similarity in socio-economic background factors does not guarantee marital happiness, while satisfactory adjustment is not precluded by ordinary dissimilarities.

In the absence of unbridgeable incompatibilities arising either from gross inadequacies in mate selection or from severe inequalities in family backgrounds (Kallmann, 1941), it appears to be the *total personality structure* of prospective mates which is the most important factor in determining the de-

FIG. 3. The M. Twins at age 19 years

FIG. 4. The N. Twins at age 28 years

gree of marital adjustment. It has been our impression that concordance as to extremely good or extremely poor marital adjustment is found more frequently in monozygotic than in dizygotic twin pairs. In fact, it occurred only in monozygotic twin pairs of the entire sample that the marital relations of both twins had been so poor that they resulted in complete disorganization of the marriages. This degree of maladjustment was illustrated by the M. twins (fig. 3), whose marriages were terminated by divorce in spite of superior mates and adequate social circumstances.

By contrast, the marriages of the N. twins (fig. 4) were extremely happy

despite equally marked differences between the respective spouses in religious, social and educational background factors.

The effect of personality factors on the relative degrees of marital adjustment or maladjustment is apt to be especially pronounced if family relations are affected by the presence of *gross psychopathology*. The severity of this effect is demonstrable in relation to both marital status and reproductivity and may be illustrated by a comparison of the marriage and fertility rates observed in the family units of normal senescent and clearly psychotic twin index cases (figs. 3–4). The data on psychotic twin index families are based on an unselected series of 953 *schizophrenic* and 75 *manic-depressive* twin patients, who required admission to a mental hospital in the State of New York and were at least 45 years old (Kallmann, 1950). Survival till the age of 45 years was a requirement for both the psychotic and non-psychotic members of the given

TABLE 3. PERCENTAGES OF CELIBATES IN NORMAL (240) AND PSYCHOTIC (300) TWIN INDEX SIBSHIPS

TYPE OF TWIN INDEX CASE	TWIN SUBJECTS OVER AGE 45				SIBS OVER AGE 45			
	Number		Celibates in Per Cent		Number		Celibates in Per Cent	
	PS	O	PS	O	PS	O	PS	O
Schizophrenic	264	111	50.7†	33.3†	59	437	50.8†	17.1*
Manic-Depressive	36	14	27.8	14.3	15	66	26.6	6.1
Senescent (Over Age 60)		240		13.3		290		11.7

PS = With Psychosis O = Without Psychosis.
* Statistically significant at 5% level.
† Statistically significant at 1% level.

sibships, while the senescent control group used was free of family units in which either a twin or a sib had ever been hospitalized for a mental disorder.

The comparatively small size of the available series of manic-depressive twin family units is explained by the fact that true cases of this type of psychosis are extremely uncommon. Therefore, the observed differences between the psychotic and non-psychotic members of the 75 sibships of this series fail to meet the criteria of statistical significance. However, the given differences show such a consistent trend that they may be taken as an indication of a diminished chance of reproduction for manic-depressive persons due to influences which are similar to those operating in schizophrenic families.

The *celibacy* rates for the three groups of family units are compared in table 3 in such a manner as to show separately for twins and sibs the lower marriage rates of psychotic persons over age 45. The percentages of celibates are highest for the psychotic members of schizophrenic units (50.7 and 50.8 per cent, respectively), but they are increased even in the non-psychotic cotwins and sibs (33.3 and 17.1 per cent). Similarly, manic-depressive twins and sibs (27.8 and 26.6 per cent) marry less frequently than do the non-psychotic persons

among their cotwins and sibs and the normal population. The increase in the celibacy rates for the non-psychotic members of schizophrenic twin family units is explained by both the effect of *schizoid* personality alterations and the operation of spontaneous *eugenic* considerations.

The changes caused by psychotic phenomena in the distribution of childless and fertile marriages are tabulated in table 4. Once again, manic-depressive and schizophrenic persons are found more frequently to remain childless when married, than is true for the normal members of their families and the general population. According to information provided by the U. S. Census of 1940,

TABLE 4. DISTRIBUTION OF MARRIED PERSONS (OVER AGE 45) WITH AND WITHOUT CHILDREN IN NORMAL (240) AND PSYCHOTIC (300) TWIN INDEX SIBSHIPS

TYPE OF TWIN INDEX CASE	WITHOUT CHILDREN				WITH CHILDREN			
	Twin Subjects		Sibs		Twin Subjects		Sibs	
	PS	O	PS	O	PS	O	PS	O
Schizophrenic	26	27	7	87	104	47	22	275
Manic-Depressive	8	1	4	9	18	11	7	53
Senescent (Over Age 60)		46		45		162		211

PS = With Psychosis O = Without Psychosis.

TABLE 5. MARITAL REPRODUCTIVITY IN NORMAL (240) AND PSYCHOTIC (300) TWIN FAMILY UNITS

TYPE OF TWIN INDEX CASE	NUMBER OF CHILDREN PER FERTILE MARRIED PERSON OVER AGE 45				NUMBER OF CHILDREN PER MARRIED PERSON OVER AGE 45			
	Twin Subjects		Sibs		Twin Subjects		Sibs	
	PS	O	PS	O	PS	O	PS	O
Schizophrenic	2.6	2.8	2.1*	3.0*	2.4	1.8	1.2*	2.3*
Manic-Depressive	2.1	2.6	2.6	3.0	1.6	2.2	2.0	2.5
Senescent (Over Age 60)		3.0		3.2		2.4		2.6

PS = With psychosis O = Without psychosis
* Statistically significant

the proportion of married persons without children in the general population over age 45 is 16.8 per cent, while the corresponding percentages for manic-depressive twins and sibs are 22.2 and 26.6, and for schizophrenic sibs, 24.6. The relatively low rate of childlessness in schizophrenic twins (9.8 per cent) is due to the extreme reduction of marriages in this group.

In view of the findings in previous comparative fertility studies (Kallmann, 1938) it is likewise in accordance with expectation that *marital reproductivity* as computed in table 5 is considerably decreased in psychotic family units, regardless of whether the number of children produced is related to fertile or to all married persons. The fertility rates of manic-depressive twin subjects seem to be even lower than the corresponding rates of schizophrenic twins,

possibly because of certain differences in their socio-economic backgrounds which usually are in favor of manic-depressive families (showing little or no social decline). Irrespective of this difference, however, it is apparent that psychotic persons have a comparatively low reproductivity rate, if they are married and fertile. In fact, both the psychotic and non-psychotic members of the given family units show lower marital fertility rates than is true for the general population. In the fertile marriages of twin subjects, the average number of children increases from 2.1 for manic-depressive cases to 2.6 for schizophrenics, in turn to 2.6 and 2.8 for the respective groups of non-psychotic cotwins, and finally to 3.0 for normal twins over age 60. The corresponding figures for the sibs rise from 2.1 and 2.6 for schizophrenic and manic-depressive subjects to 3.0 for the marriages of their non-psychotic sibs, and to 3.2 for the sibs of senescent twin subjects. Most of these differences appear rather convincing, although their magnitude cannot be demonstrated as statistically significant for all of them. According to 1940 Census data, the corresponding fertility rate for the white population of the State of New York is 3.37 children.

It is justified to say, therefore, that psychotic individuals marry less frequently, tend more often to remain childless when married, and produce fewer children if fertile, than is true for their normal sibs and the general population. In addition, there appears to be less chance of finding a mate for a non-psychotic member of a psychotic index family if the relationship is to a psychotic cotwin rather than to a psychotic brother or sister.

In conclusion, it may be stated that the twin study method provides promising interdisciplinary and procedurally controlled approaches to the complex problems of marriage and family relations. The potential applications include investigations of the range of variations in mate selection, biological and cultural background factors, general personality structure and the effect of psychopathological deviations in relation to the prospects of marital adjustment, reproductiveness and successful socialization during different periods of adult life including senescence.

Various avenus of approach to the given scope of marriage problems have been demonstrated by means of a tentative comparative analysis of histories of normal (senescent) and psychotic (schizophrenic, manic-depressive) twin index pairs and their sibships. For reasons beyond our control, however, it has not been possible to procure statistically representative data on all observable differences in mate selection and marital adjustment from the available sample. The immediate objective of the present survey has been to show the methodological potentialities and limitations of twin studies in the field of family relations rather than to offer comprehensive statistics on topics which call for long-range investigation and interdisciplinary team work. In any case, the potential usefulness of the twin study method for such inquiries is unquestionable in spite of some undeniable limitations. The main disadvantage of the method may be seen in the fact that the usual dissimilarities in per-

sonality, education and mate selection, as they are observable either between twin partners or among other members of a sibship unit, do not cover the entire range of theoretically expected differences.

Nevertheless, it would seem definitely indicated to organize well-planned twin research in the field of family relations. It is the consensus of all branches of science that the family is intrinsic to human living, firmly established in biological laws, and indispensable to the maintenance of human society. By effecting a close cooperation between the social and biological sciences, jointly organized twin studies offer excellent opportunities toward the common goal of improving the utilization of the human capacity for adjustment, marital happiness, and survival.

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1951—PART 4

THIS section, prepared by Dr. V. Rae Phelps, continues the list of current research articles and books of special interest to students of human heredity, which was started with the first issue of Volume I, covering the year 1949. The present list includes publications issued in 1951 (Part 4) and 1952 (Part 1). For further information regarding the organization of the Bibliography, see Parts 3 and 4 of the 1950 list published in Volume 3.

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